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(54) **IMIDAZOPYRIDINE COMPOUNDS**

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CPC ***C07D 471/04*** (2013.01); ***C07D 453/02*** (2013.01); ***C07D 519/00*** (2013.01)

(58) **Field of Classification Search**
None
See application file for complete search history.

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(57) **ABSTRACT**

An excellent drug for treating or preventing cardiovascular diseases, based on cGMP production enhancing action due to soluble guanylate cyclase activating action, is provided. It was found that imidazopyridine compounds having a carbamoyl group at the 3-position and a substituent bonded at the 8-position via an oxygen atom in an imidazo[1,2-a]pyridine skeleton exhibits a cGMP production enhancing action by a potent soluble guanylate cyclase activating action, and is useful as a drug for treating or preventing various soluble guanylate cyclase-related cardiovascular diseases, thereby completing the present invention.

15 Claims, No Drawings

IMIDAZOPYRIDINE COMPOUNDS

TECHNICAL FIELD

The present invention relates to imidazopyridine compounds useful as active ingredients of pharmaceutical compositions, for example, pharmaceutical compositions for treating or preventing various cardiovascular diseases, which have soluble guanylate cyclase (sGC) activation based on improvement of cGMP signals.

BACKGROUND ART

cGMP (cyclic guanosine monophosphate) is an important intracellular messenger and is involved in the regulation of various physiological phenomena such as relaxation and proliferation of smooth muscle cells, aggregation and adhesion of platelets, and signaling of nerve cells, through the control of a cGMP-dependent protein kinase, a phosphodiesterase, and ion channels. The cGMP is catalytically produced from guanosine triphosphate (GTP) by a guanylate cyclase in the response to various extracellular and intracellular stimulation. There have been reported two groups of guanylate cyclases to date, that is, particulate guanylate cyclases stimulated by peptidic messengers (for example, atrial natriuretic peptides, brain natriuretic peptides, and the like) and soluble guanylate cyclase stimulated by nitric oxide (NO).

The sGC is one of the most important target molecules of NO that is a messenger which plays a very important role in maintaining homeostasis of the body, and forms an NO/sGC/cGMP pathway. It has been reported that this enzyme is constituted with two subunits, each of the heterodimer contains one heme, and the heme plays a central role in an activation mechanism. It is believed that when NO binds to the iron in the heme, the enzyme is changed to an active conformation. Therefore, there is no stimulation by NO with enzyme preparations containing no heme. Although carbon monoxide (CO) may also bind to the iron in the heme, but the stimulation by CO is significantly lower than that by NO.

The sGC is constituted with α and β subunits. Analysis of cGC from tissue-specific distributions and in different growth steps demonstrated multiple isotypes with different subunit compositions. The distribution of the respective subunits have been studied with mammals including a human, and it has been widely recognized that al and β1 subunits are expressed in many tissues and the α1β1 forms have a pattern of a heterodimer that works functionally. α2 subunits have been also recognized, which exist fewer organs as compared to the α1, and it has been reported that the α2 subunits are expressed more frequently than α1 in the brain, the lung, the colon, the heart, the spleen, the uterus, and the placenta. Subunits called α3 and β3 were isolated from the human brain, but are homologous to α1 and β1. In addition, according to recent studies, α2i subunits which contain an insert in the catalytic domain have identified. All of the subunits exhibit high homology in catalytic domain regions.

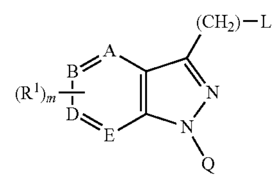
Under pathophysiological conditions, it has been reported that there is inhibition of the production of or promotion of the degradation of sGC activating factors such as NO for the reasons of increased generation of free radicals, and the like. With a decrease in the sGC activating factors, NO/sGC/cGMP signals are attenuated, which results in, for example, increased blood pressure, platelet activation, or increased cell proliferation and cell adhesion. As a result, a variety of cardiovascular diseases, specifically, hypertension (including pulmonary hypertension), atherosclerosis, peripheral arterial diseases, lumbar spinal canal stenosis, intermittent claudication, critical limb ischemia, stable or unstable angina pectoris, heart failure, thrombosis, stroke, and sexual dysfunction occur. Therefore, a new drug having a mechanism of selectively activating sGC is believed to have the potential of normalizing cGMP production, and thus or prevent such diseases can be treated or prevented.

As the sGC activator, there have been known, for example, "heme-dependent stimulants" which activate sGC depending on heme groups, such as NO donors as described later and the like, and "heme-independent activators" which are independent on the heme groups (Non-Patent Document 2).

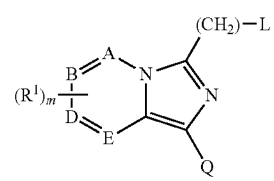
For the activation of sGC, a group of compounds called NO donors such as organic nitrates have been widely used so far. These compounds are heme-dependent stimulants which activate sGC by being metabolized in vivo to produce NO, which then binds to a central iron atom of a heme. However, the NO donors have critical disadvantages such as expression of a resistance, a decrease in the effects and the like is expressed in addition to side-effects, and therefore, there is a demand for a novel sGC activator that does not have these disadvantages.

For example, compounds of the following formulae (a) to (c) have been reported as compounds having sGC activating action (Patent Document 1).

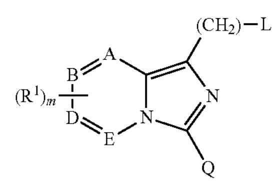
[Chem. 1]



(a)



(b)



(c)

(Compounds of the formula (a) are pyrazolo[3,4]fused bicyclic compounds, and compounds of formulae (b) and (c) are imidazo[1,5]fused bicyclic compounds. Further, Q means substituted heterocycle in any one of the formulae (a) to (c). For details, refer to the document.)

In this document, there is no disclosure or suggestion of compounds having an imidazo[1,2-a]pyridine skeleton.

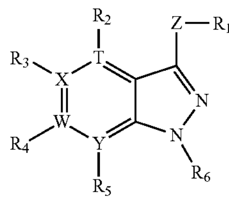
In addition, pyrazole derivatives or pyrazolo[3,4-b]pyridine derivatives are disclosed as the sGC activating compounds in International Publications WO 2000/06569, WO 2000/21954, WO 2001/83490, WO 2003/004503, WO 2003/095451, WO 2003/086407, WO 2003/097063, WO 2007/124854, WO 2007/128454, WO 2008/031513, WO

2008/061657, WO 2010/078900, and WO 2010/079120. However, in any of these documents, there is no disclosure or suggestion of compounds having an imidazo[1,2-a]pyridine skeleton.

Furthermore, compounds of the following formula (d) have been reported as sGC activators (Patent Document 2).

[Chem. 2]

(d)



(wherein Z is O, S, or $N(R_7)$, R_7 is H or alkyl, and R_6 is aryl, arylalkenyl, heterocycle, -(alkenyl)-(heterocycle), or heterocycloalkyl).

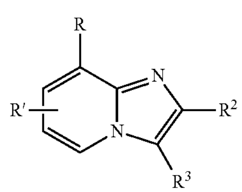
However, this document does not disclose or suggest compounds having an imidazo[1,2-a]pyridine skeleton.

As other sGC activators, 1H-pyrazole-5-carboxylic acid derivatives (Patent Document 3), biaryl derivatives (Patent Document 4), and benzylindazole derivatives (Non-Patent Document 1) have been reported.

Furthermore, compounds having an imidazopyridine skeleton, for example, compounds of the following formula (e) useful for the treatment of gastrointestinal ulcer as an H+/K+-ATPase enzyme inhibitors have been reported (Non-Patent Document 3).

[Chem. 3]

(e)



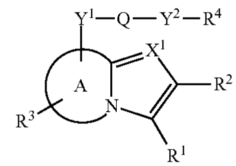
(wherein R means substituted alkoxy group, R' means H or phenethyl, R^2 means H or lower alkyl, and R^3 means substituted alkyl or the like. For details, refer to the document).

This document does not disclose or suggest sGC activators, and compound of formula (I) of the present invention as described later has a different structure from that of the compound of the formula (e) in that the compound of formula (I) has an aminocarbonyl group at the 3-position.

Moreover, compounds of the formula (f) useful for the treatment of allergy, inflammation, pain, or the like as bradykinin antagonists have been reported (Patent Document 5).

[Chem. 4]

(f)



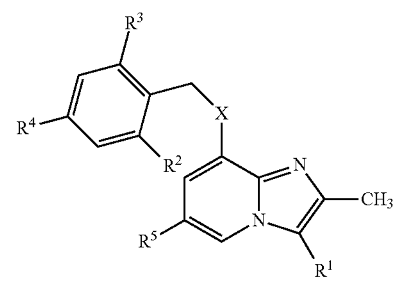
(wherein R^1 to R^3 each mean hydrogen, lower alkyl, or the like, R^4 means an aryl group which may have a suitable substituent, or the like, Q means O, NH, or the like, X^1 means N or C—R^5, Y^1 and Y^2 each mean a single bond or a lower alkylene group, and Ring A means 6-membered nitrogen-containing heterocycle. For details, refer to the document).

This document does not disclose or suggest sGC activators, and the compound of formula (I) of the present invention as described later has a different structure from that of the compound of formula (f) in that the compound of formula (I) has an aminocarbonyl group at the 3-position.

Furthermore, compounds of formula (g) with H+/K+-ATPase enzyme inhibitory activities and useful for the inhibition of gastric acid secretion have been reported (Patent Document 6).

[Chem. 5]

(g)



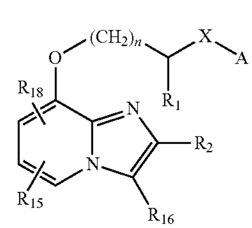
(wherein R^1 is CH_3 or CH_2OH, R^2 and R^3 are each lower alkyl, R^4 is H or halogen, R^5 is H, halogen, or lower alkyl, and X is NH or O. For details, refer to the document).

This document does not disclose or suggest sGC activators, and the compound of formula (I) of the present invention as described later have different structure from that of the compound of formula (g) in that the compound of formula (I) has an aminocarbonyl group at the 3-position.

Moreover, compounds of formula (h) have been reported as cardiac ion channel modulators and as antiarrhythmic agents (Patent Document 7).

[Chem. 6]

(h)

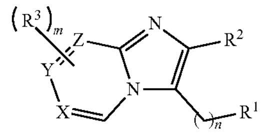


(wherein R_2, R_{15}, R_{16}, and R_{18} are each Br, Cl, F, carboxy, H, —OH, hydroxymethyl, or the like, and R_1 is H, C_{1-6} alkyl, aryl, benzyl, or the like. For details, refer to the document).

This document does not disclose or suggest sGC activators, and the compound of formula (I) of the present invention as described later have different structure from that of the compound of formula (h) in that the compound of formula (I) has an aminocarbonyl group at the 3-position.

In addition, compound of formula (i) useful as a drug for treating bacterial infection, particularly tuberculosis, have been reported (Patent Document 8).

[Chem. 7]



(i)

(wherein X, Y, and Z are each CH or the like, n is 0 or the like, m is 1 or the like, R^1 is —C(O)N(R^4)$_2$ or the like, R^2 is C_{1-10} alkyl or the like, R^3 is —OR^6 or the like, and R^6 is C_{1-10} alkyl optionally substituted, or the like. For details, refer to the document).

This document specifically discloses a compound, in which X, Y, and Z are each CH, n is 0, R^1 is —C(O)N(R^4)$_2$, R^2 is C_{1-10} alkyl, m is 1, R^3 is —OR^6, and R^6 is H, methyl, or difluoromethyl. However, this document does not disclose or suggest sGC activators, and the compound of formula (I) of the present invention as described later has a different structure from that of the compounds disclosed in this document in that the substituent A^1 is lower alkyl.

RELATED ART

Patent Document

[Patent Document 1] Pamphlet of International Publication WO 2008/031513
[Patent Document 2] Pamphlet of International Publication WO 2003/076408
[Patent Document 3] Pamphlet of International Publication WO 2000/027394
[Patent Document 4] Pamphlet of International Publication WO 2001/032604
[Patent Document 5] JP-A-H7-242666
[Patent Document 6] Pamphlet of International Publication WO 1998/37080
[Patent Document 7] Pamphlet of International Publication WO 2001/096335
[Patent Document 8] Pamphlet of International Publication WO 2011/113606
[Non-Patent Document 1] Blood (1994), Vol. 84, p. 4226
[Non-Patent Document 2] Journal of Cardiovascular Pharmacology (2010), Vol. 56, p. 229
[Non-Patent Document 3] Journal of Medicinal Chemistry (1985), Vol. 28, p. 876

DISCLOSURE OF INVENTION

Technical Problem

Problems to Be Solved by the Invention

Imidazopyridine compounds, useful as active ingredients of pharmaceutical compositions, for example, pharmaceutical compositions for treating or preventing various cardiovascular diseases, which have soluble guanylate cyclase (sGC) activities based on improvement of cGMP signals, are provided.

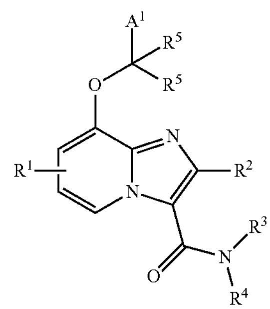
Means for Solving the Problems

The present inventors have made extensive studies on compounds having sGC activation, and as a result, they have found that compounds of formula (I) which are imidazo[1,2-a]pyridine compounds having a carbamoyl group at the 3-position and a substituent bonded at the 8-position via an oxygen atom, and a salt thereof have sGC activation, and are useful as active ingredients of pharmaceutical compositions for treating or preventing various sGC-related cardiovascular diseases, in particular, peripheral arterial diseases, intermittent claudication, critical limb ischemia, and hypertension (including pulmonary hypertension), thereby completing the present invention.

That is, the present invention relates to a compound of formula (I) or a salt thereof, and pharmaceutical compositions comprising the compound of formula (I) or a salt thereof and a pharmaceutically acceptable excipient.

[Chem. 8]

(I)



[the symbols in the formula have the following meanings:

A^1: R^0, —R^{00}-(aryl), halogeno-lower alkyl, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted aryl, or optionally substituted heteroaryl,

R^0: the same as or different from each other, and each representing lower alkyl,

R^{00}: the same as or different from each other, and each representing lower alkylene,

R^1: H, R^0, halogen, —CN, —CO_2H, —CO_2R^0, or —R^{00}—OH,

R^2: H, R^0, C_{3-6} cycloalkyl, or halogeno-lower alkyl,

R^3: H, R^0, —R^{00}—CO_2H, or —R^{00}—CO_2R^0,

R^4: —Y-A^2 or A^3, or R^3 and R^4, together with N atom to which they are both bonded, may form a nitrogen-containing saturated heterocycle optionally substituted with at least one group selected from the group consisting of —OH, —R^{00}—OH, —CO_2H, —CO_2R^0, and phenyl,

Y: C_{1-10} alkylene optionally substituted with at least one group selected from Group G^2, C_{2-10} alkenylene optionally substituted with at least one group selected from Group G^2, or —SO_2-(lower alkylene optionally substituted with at least one group selected from Group G^2)-,

Group G^2: —CO_2H, —CO_2R^0, —OH, —OR^0, —O—CO—R^0, —OSi(R^0)$_3$, —NH_2, —NHR^0, —N(R^0)$_2$, —NH—CO—R^0, —SR^0, —CO—NH—SO_2—R^0, optionally substituted aryl, and optionally substituted heteroaryl,

A^2: H, —OH, —O-(aryl), —CO—R^0, —CO—R^{00}—OH, —CO_2—R^{00}-(aryl), —CO—NH_2, —CO—NHR^0, —CO—$N(R^0)_2$, optionally substituted cycloalkyl, optionally substituted heterocycloalkyl, optionally substituted aryl, or optionally substituted heteroaryl,

A^3: H, cycloalkyl optionally substituted with at least one group selected from Group G^1, heterocycloalkyl optionally substituted with at least one group selected from Group G^1, aryl optionally substituted with at least one group selected from Group G^1, or heteroaryl optionally substituted with at least one group selected from Group G^1,

Group G^1: R^0, halogen-lower alkyl, —R^{00}—OH, halogen, oxo, —NO_2, —OH, —OR^0, —O—R^{00}—$N(R^0)_2$, —NH_2, —CO—R^0, —CO—R^{00}—OH, —CO_2H, —CO_2R^0, —CO—NH_2, —CO—NHR^0, —CO—$N(R^0)_2$, —CO_2—R^{00}-(phenyl), —SO_2—R^0, —SO_2—NH_2, —SO_2—NHR^0, —SO_2—$N(R^0)_2$, —SO_2—R^{00}—CO_2H, —SO_2—R^{00}—CO_2R^0, —SO_2-(phenyl), —SO_2—R^{00}-(phenyl), —R^{00}—CO_2H, —R^{00}—CO_2R^0, —R^{00}—CO—NH_2, —R^{00}—CO—NHR^0, —R^{00}—CO—$N(R^0)_2$, —R^{00}—NH_2, —R^{00}—NHR^0, —R^{00}—$N(R^0)_2$, —R^{00}-(phenyl), —R^{00}-(phenylene)-R^0, —R^{00}-(cycloalkyl), —R^{00}-(heterocycloalkyl), —R^{00}-(monocyclic nitrogen-containing heteroaryl), cycloalkyl, phenyl, -(phenylene)-R^0, -(phenylene)-CO_2H, -(phenylene)-CO_2R^0, -(pyridinediyl)-CO_2H, -(pyridinediyl)-CO_2R^0, -(piperidinediyl)-R^0, -(phenylene)-R^{00}—CO_2H, —R^{00}-(phenylene)-CO_2H, —R^{00}-(phenylene)-CO_2R^0, monocyclic nitrogen-containing heteroaryl, and heterocycloalkyl, and

R^5: the same as or different from each other, and each representing H or R^0,

provided that the compound of the formula (I) is neither 8-(benzyloxy)-2-methylimidazo[1,2-a]pyridine-3-carboxamide nor 8-(benzyloxy)-2-methylimidazo[1,2-a]pyridin-3-yl](piperazin-1-yl)methanone)].

Furthermore, unless specifically described otherwise, when symbols in one formula in the present specification are also used in other formulae, same symbols denote same meanings.

Moreover, the present invention relates to pharmaceutical compositions for treating sGC-related cardiovascular diseases, which include compound of formula (I) or a salt thereof. Further, said pharmaceutical compositions include agents for treating sGC-related cardiovascular diseases, which includes compounds of the formula (I) or a salt thereof.

The present invention further relates to use of compound of formula (I) or a salt thereof for preparation of pharmaceutical compositions for treating or preventing sGC-related cardiovascular diseases, use of compound of formula (I) or a salt thereof for treating or preventing sGC-related cardiovascular diseases, compound of the formula (I) or a salt thereof for treating or preventing sGC-related cardiovascular diseases, and methods for treating or preventing sGC-related cardiovascular diseases, comprising administering to a subject an effective amount of compound of formula (I) or a salt thereof. In this regard, the "subjects" refer to humans or other animals in need of the prevention or treatment, and in a certain embodiment, humans in need of the prevention or treatment.

Effects of the Invention

Compound of formula (I) has an sGC activation and can be used as active ingredients of pharmaceutical compositions for treating or preventing sGC-related cardiovascular diseases, for example, hypertension, atherosclerosis, lumbar spinal canal stenosis, peripheral arterial diseases, intermittent claudication, critical limb ischemia, stable or unstable angina pectoris, heart failure, thrombosis, stroke, sexual dysfunction, pulmonary hypertension, or the like.

EMBODIMENTS FOR CARRYING OUT THE INVENTION

Hereinbelow, the present invention will be described in detail.

In the present specification, the "cardiovascular disease" refers to a disease based on the abnormal symptoms of circulatory organs such as heart, blood vessels, and the like. Among these, the "sGC-related cardiovascular disease" is known to be involved in an NO/sGC/cGMP system, and is a cardiovascular disease that can be treated or prevented by sGC activation. Examples thereof include hypertension (including pulmonary hypertension), atherosclerosis, lumbar spinal canal stenosis, peripheral arterial disease, intermittent claudication, critical limb ischemia, stable or unstable angina pectoris, heart failure, thrombosis, stroke, sexual dysfunction, and the like. In another embodiment, the "sGC-related cardiovascular disease" is intermittent claudication and critical limb ischemia caused by peripheral arterial diseases. In another embodiment, it is intermittent claudication caused by peripheral arterial diseases, and in another embodiment, critical limb ischemia caused by peripheral arterial diseases.

Here, examples of the peripheral arterial diseases include occlusive thrombotic vasculitis, peripheral arterial occlusive disease, Raynaud's disease, and Raynaud's syndrome.

The "peripheral arterial disease" is a disorder in which stenosis and occlusions caused by atherosclerosis, thrombosis and other impairments produce deficient blood flow, especially in the lower limbs. The symptoms are cold leg or feet, intermittent claudication, lower limb pain and critical limb ischemia (lower limb ulcers and necrosis). Diagnosis and treatment guidelines for peripheral arterial disease can be found in the following reference.

Eur. J. Vasc. Endovasc. Surg, 2007, 33(1), S1

"Intermittent claudication" means in one embodiment, intermittent claudication caused by peripheral arterial diseases, and in another embodiment intermittent claudication caused by peripheral arterial occlusive disease.

"Critical limb ischemia" means in one embodiment, critical limb ischemia caused by peripheral arterial diseases, and in another embodiment critical limb ischemia caused by peripheral arterial occlusive disease.

Further, the "sGC-related cardiovascular disease" means in one embodiment, hypertension or pulmonary hypertension.

The "hypertension" means, in a one embodiment, essential hypertension, abnormal circadian blood pressure variability, renal parenchymal hypertension, renovascular hypertension, primary aldosteronism, Cushing's syndrome, hibernoma, or hypertension associated with endocrine diseases. The "pulmonary hypertension" is, in a certain embodiment, pulmonary arterial pulmonary hypertension, pulmonary hypertension associated with heart diseases, pulmonary hypertension associated with lung diseases such as chronic obstructive pulmonary diseases or interstitial lung diseases, or pulmonary hypertension associated with chronic thrombotic or obstructive diseases.

The "lower alkyl" is a monovalent group formed by the removal of any one hydrogen atom from a linear or branched saturated hydrocarbon having 1 to 6 carbon atoms (hereinafter simply referred to as C_{1-6}), and it is specifically methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, n-pentyl, n-hexyl, or the like, in another embodiment, C_{1-4} alkyl, and in a still another embodiment, methyl, ethyl, n-propyl, or isopropyl.

The "C_{1-10} alkylene" is a divalent group formed by the removal of any two hydrogen atoms from a linear or branched saturated hydrocarbon having 1 to 10 carbon atoms, and it is, for example, methylene, ethylene, trimethylene, tetramethylene, pentamethylene, hexamethylene, propylene, methylmethylene, ethylethylene, 1,2-dimethylethylene, 1,1,2,2-tetramethylethylene, or the like, in another embodiment, methylene or ethylene, and in still another embodiment, methylene.

The "lower alkylene" means "C_{1-6} alkylene" among the "C_{1-10} alkylene" above, and it is, in a certain embodiment, methylene, ethylene, trimethylene, or the like, and in another embodiment, methylene or ethylene.

The "C_{2-10} alkenylene" is a divalent group formed by the removal of any two hydrogen atoms from a linear or branched hydrocarbon having a double bond and 2 to 10 carbon atoms. It is, in a certain embodiment, ethylidene, propenylene, or butenylene, in another embodiment, ethylidene, and in still another embodiment, trans-1,2-ethylidene.

The "cycloalkyl" is a C_{3-10} saturated hydrocarbon ring group, which may have a bridge, may be combined with another cycloalkyl to form a spiro ring, may partly have unsaturated bond and may be fused with a ring selected from a benzene ring, a furan ring, a thiophene ring, and a pyrrole ring. Examples of the "cycloalkyl" include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, adamantyl, indanyl, tetrahydronaphthyl, indanyl, indenyl, cyclohexenyl, spiro[3.5]nonyl, dihydrocyclopentathienyl, dihydrocyclopentafuranyl, dihydrocyclopentapyrrolyl, or the like. In a certain embodiment, "cycloalkyl" is a monocyclic C_{3-8} cycloalkyl, in another embodiment, cyclohexyl, and in still another embodiment, indanyl. Here, when fused with a pyrrole ring, the cycloalkyl is fused to a carbon-carbon bond of the pyrrole ring.

The "halogen" is F, Cl, Br, or I, and in a certain embodiment, F or Cl.

The "halogeno-lower alkyl" is C_{1-6} alkyl substituted with one or more halogen atoms, in a certain embodiment, C_{1-6} alkyl substituted with 1 to 5 halogen atoms, and in another embodiment, difluoromethyl or trifluoromethyl.

The "aryl" is a C_{6-14} monocyclic to tricyclic aromatic hydrocarbon ring group, in a certain embodiment, phenyl or naphthyl, and in another embodiment, phenyl.

The "heteroaryl" means a 5- to 14-membered, monocyclic to tricyclic aromatic heterocyclic group containing 1 to 6 hetero atoms selected from N, O, and S as a ring-constituting atom. The "heteroaryl" is, in a certain embodiment, monocyclic heteroaryl, for example, pyridyl, pyrimidinyl, triazinyl, furyl, thienyl, pyrrolyl, imidazolyl, pyrazolyl, tetrazolyl, oxazolyl, thiazolyl, isoxazolyl, or the like, in another embodiment, bicyclic heteroaryl, for example, indolyl, quinolyl, quinoxalinyl, or the like, and in still another embodiment, pyridyl, thienyl, or indolyl.

The "nitrogen-containing saturated heterocycle" is a 5- to 8-membered saturated heterocycle that contains one nitrogen atom as a ring-constituting atom and may further contain one or two hetero atoms selected from N, O, and S, and it may be fused with a benzene ring. Examples of the nitrogen-containing saturated heterocyclic group include azetidinyl, pyrrolidinyl, piperidyl, piperazinyl, azepanyl, diazepanyl, azocanyl, morpholinyl, thiomorpholinyl, tetrahydropyridinyl, and groups formed by fusion of any one of these ring groups with a benzene ring. The nitrogen-containing saturated heterocyclic group is, in another embodiment, pyrrolidinyl, piperidyl, piperazinyl, or indolin-1-yl, and in still another embodiment, pyrrolidinyl or indolin-1-yl.

The "monocyclic nitrogen-containing heteroaryl" means a monocycle containing a nitrogen atom as a ring-constituting atom among the "heteroaryl" above, and it is, in a certain embodiment, pyridyl, pyrimidinyl, thiazolyl, pyrazolyl, or oxadiazolyl, and in another embodiment, pyridyl.

The "heterocycloalkyl" is a 3- to 14-membered, saturated or partially unsaturated heterocyclic group that contains 1 to 6 hetero atoms selected from N, O, and S as a ring-constituting atom, and it may be bridged or fused. The "heterocycloalkyl" is, in a certain embodiment, azetidinyl, pyrrolidinyl, imidazolidinyl, piperidyl, pyrazolyl, piperazinyl, morpholinyl, thiomorpholyl, oxazolidinyl, tetrahydrofuranyl, tetrahydropyranyl, 1,3-dioxanyl, 1,4-dioxanyl, indolinyl, dihydrobenzofuranyl, or quinuclidinyl, and in another embodiment, pyrrolidinyl, piperidyl, or indolinyl.

The expression "optionally substituted" means non-substitution or substitution with 1 to 5 substituents. It is, in a certain embodiment, non-substitution or substitution with 1, 2, or 3 substituents, in another embodiment, non-substitution or substitution with 1 or 2 substituents, in still another embodiment, non-substitution or substitution with one substituent, in a further still another embodiment, substitution with two substituents, in a further still another embodiment, substitution with one substituent, and in a further still another embodiment, non-substitution. If it has a plurality of substituents, the substituents may be the same as or different from each other.

Examples of substituents of the "optionally substituted cycloalkyl", "optionally substituted heterocycloalkyl", "optionally substituted aryl", or "optionally substituted heteroaryl" in A^1 include, in a certain embodiment, a group selected from the group consisting of halogen, —CN, lower alkyl, and halogeno-lower alkyl. A^1 is, in a certain embodiment, cycloalkyl, heterocycloalkyl optionally substituted with one or more F atoms, aryl optionally substituted with one or more F atoms, or heteroaryl optionally substituted with one or more F atoms. Further, A^1 is, in another embodiment, unsubstituted cycloalkyl, unsubstituted heterocycloalkyl, unsubstituted aryl, or unsubstituted heteroaryl.

Examples of the substituents of the "optionally substituted cycloalkyl", "optionally substituted heterocycloalkyl", "optionally substituted aryl", and "optionally substituted heteroaryl" in A^2 include in a certain embodiment, a group selected from the group consisting of —OH, oxo, —OR^0, —O—R^{00}—CO_2R^0, —O—R^{00}—CO_2H, CO_2H, —CO—R^0, —NH_2, —NHR^0, —$N(R^0)_2$, —NH—R^{00}—OH, —CO_2H, —CO_2R^0, —SO_2—R^0, —R^{00}—CO_2H, CO_2H, —R^{00}—CO_2R^0, halogen, phenyl, morpholyl, (piperidyl optionally substituted with carboxy or alkoxycarbonyl), R^0, and halogeno-lower alkyl. A substituent is in another embodiment, R^0, halogen, or —CO_2H, and in still another embodiment, —CO_2H.

A substituted examples of the substituent of the "optionally substituted aryl" and "optionally substituted heteroaryl" in Group G^2 is, in a certain embodiment, a group selected from the group consisting of R^0, —OH, halogen, oxo, —CO_2H, and —OR^0. The substituent is, in another embodiment, methyl, F, Cl, or methoxy.

Group G^2 is, in one embodiment, unsubstituted aryl and unsubstituted heteroaryl.

Certain embodiments of the present invention are shown below.

(1) The compound of formula (I) or a salt thereof, wherein A^1 is cycloalkyl, or phenyl optionally substituted with one or

more halogen atoms; in another embodiment, the compound of formula (I) or a salt thereof, wherein A^1 is cyclohexyl, or phenyl optionally substituted with one or more F atoms; in still another embodiment, the compound of the formula (I) or a salt thereof, wherein A^1 is cyclohexyl; in further still another embodiment, the compound of the formula (I) or a salt thereof, wherein A^1 is phenyl optionally substituted with one or more F atoms; and in further still another embodiment, the compound of the formula (I) or a salt thereof, wherein A^1 is cyclohexyl, 2-fluorophenyl, 2,3-difluorophenyl, 2,6-difluorophenyl, or 2,3,6-trifluorophenyl.

(2) The compound of formula (I) or a salt thereof, wherein R^1 is H.

(3) The compound of formula (I) or a salt thereof, wherein R^2 is methyl.

(4) The compound of formula (I) or a salt thereof, wherein R^3 is H.

(5) The compound of formula (I) or a salt thereof, wherein R^4 is —Y-A^2; and in another embodiment, the compound of formula (I) or a salt thereof, wherein R^4 is A^3.

(5-1) The compound of formula (I) or a salt thereof, wherein R^4 is —Y-A^2, and A^2 is H, —OH, or —$CONH_2$, or phenyl, pyridyl, pyrimidinyl, triazinyl, pyrrolyl, pyrazolyl, thienyl, furyl, thiazolyl, oxazolyl, isoxazolyl, isoxadiazolyl, tetrazolyl, quinoxalinyl, piperidyl, piperazyl, morpholyl, thiomorpholyl, tetrahydropyranyl, tetrahydrothiopyranyl, quinuclidyl, or monocyclic C_{3-8} cycloalkyl, each of which is optionally substituted with at least one group selected from the group consisting of —OH, oxo, —OR^0, —O—R^{00}—CO_2R^0, —O—R^{00}—CO_2H, —CO—R^0, —NH_2, —NHR^0, —$N(R^0)_2$, —NH—R^{00}—OH, —CO_2H, —CO_2R^0, —SO_2—R^0, —R^{00}—CO_2H, —R^{00}—CO_2R^0, halogen, phenyl, morpholyl, (piperidyl optionally substituted with carboxy or alkoxycarbonyl), R^0, and halogeno-lower alkyl; in another embodiment, the compound of formula (I) or a salt thereof, wherein R^4 is —Y-A^2, and A^2 is H, pyridyl, or phenyl optionally substituted with at least one group selected from the group consisting of R^0, halogen, and —CO_2H; and in still another embodiment, the compound of formula (I) or a salt thereof, wherein R^4 is —Y-A^2, and A^2 is H, pyridyl, or phenyl optionally substituted with —CO_2H.

(5-2) The compound of formula (I) or a salt thereof, wherein R^4 is —Y-A^2, and Y is C_{1-10} alkylene optionally substituted with at least one group selected from Group G^2, C_{2-10} alkenylene optionally substituted with at least one group selected from Group G^2, or —SO_2— (lower alkylene optionally substituted with at least one group selected from Group G^2)-; in another embodiment, the compound of formula (I) or a salt thereof, wherein R^4 is —Y-A^2, and Y is C_{1-10} alkylene optionally substituted with at least one group selected from Group G^2 or C_{2-10} alkenylene optionally substituted with at least one group selected from Group G^2; in still another embodiment, the compound of formula (I) or a salt thereof, wherein R^4 is —Y-A^2, and Y is C_{1-6} alkylene optionally substituted with at least one group selected from Group G^2. Here, Group G^2 is, in a certain embodiment, phenyl, pyridyl, thienyl, cyclopentyl, cyclohexyl, —CO_2H, —CO_2R^0, —OH, and —OR^0, each of which is optionally substituted with at least one group selected from the group consisting of halogen, —OR^0, and R^0; in another embodiment, pyridyl, phenyl, and cyclohexyl; in still another embodiment, —CO_2H, —CO_2R^0, —OH, and —OR^0; and in a further still another embodiment, —CO_2H, —CO_2R^0, and —OH.

(5-3) The compound of formula (I) or a salt thereof, wherein R^4 is A^3, and A^3 is cycloalkyl or heterocycloalkyl; in another embodiment, the compound of formula (I) or a salt thereof, wherein R^4 is A^3 and A^3 is heterocycloalkyl; in still another embodiment, the compound of formula (I) or a salt thereof, wherein R^4 is A^3 and A^3 is cycloalkyl; in a further still another embodiment, the compound of formula (I) or a salt thereof, wherein R^4 is A^3, and A^3 is pyrrolidyl optionally substituted with at least one group selected from Group G^1, piperidyl optionally substituted with at least one group selected from Group G^1, or piperazyl optionally substituted with at least one group selected from Group G^1; in a further still another embodiment, the compound of formula (I) or a salt thereof, wherein R^4 is A^3, and A^3 is monocyclic C_{3-8} cycloalkyl optionally substituted with at least one group selected from Group G^1, or indanyl optionally substituted with at least one group selected from Group G^1; in a further still another embodiment, the compound of formula (I) or a salt thereof, wherein R^4 is A^3, A^3 is piperidyl optionally substituted with at least one group selected from Group G^1, or pyrrolidyl optionally substituted with at least one group selected from Group G^1; and in a further still another embodiment, the compound of formula (I) or a salt thereof, wherein R^4 is A^3, and A^3 is indanyl optionally substituted with at least one group selected from Group G^1. Here, the compound of formula (I) or a salt thereof, wherein Group G^1 includes, in a certain embodiment, R^0, —R^{00}—OH, halogen, oxo, —OH, —OR^0, —CO—R^0, —CO—R^{00}—OH, —CO_2H, —CO_2R^0, —CO—NH_2, —CO_2—R^{00}-(phenyl), —SO_2—R^0, —SO_2—NH_2, —SO_2—NHR^0, —SO_2—R^{00}—CO_2H, —SO_2—R^{00}—CO_2R^0, —SO_2-(phenyl), —R^{00}—CO_2H, —R^{00}—CO_2R^0, —R^{00}-(phenyl), cycloalkyl, phenyl, -(phenylene)-CO_2R^0, -(piperidinediyl)-R^0, —R^{00}-(phenylene)-CO_2H, and —R^{00}-(phenylene)-CO_2R^0; Group G^1 is, in another embodiment, halogen, —OH, —CO_2H, —CO_2R^0, —CO_2—R^{00}-(phenyl), —SO_2—R^{00}—CO_2R^0, —R^{00}—CO_2H, —R^{00}—CO_2R^0, and phenyl; in still another embodiment, R^0; in a further still another embodiment, halogen, R^0, —CO_2H, and —OH; in a further still another embodiment, halogen, R^0, —CO_2H, and —OH; and in a further still another embodiment, —OH, phenyl, and —SO_2—NH_2.

(5-4) The compound of formula (I) or a salt thereof, which is selected from a compound group including the following (5-5) and (5-6).

(5-5) The compound of formula (I) or a salt thereof, wherein R^4 is A^3, A^3 is heterocycloalkyl, and Group G^1 is R^0, —R^{00}—OH, halogen, oxo, —OH, —OR^0, —CO—R^0, —CO—R^{00}—OH, —CO_2H, —CO_2R^0, —CO—NH_2, —CO_2—R^{00}-(phenyl), —SO_2—R^0, —SO_2—NH_2, —SO_2—NHR^0, —SO_2—R^{00}—CO_2H, —SO_2—R^{00}—CO_2R^0, —SO_2-(phenyl), —R^{00}—CO_2H, —R^{00}—CO_2R^0, —R^{00}-(phenyl), cycloalkyl, phenyl, -(phenylene)-CO_2R^0, -(piperidinediyl)-R^0, —R^{00}-(phenylene)-CO_2H, and —R^{00}-(phenylene)-CO_2R^0.

(5-6) The compound of formula (I) or a salt thereof, wherein R^4 is A^3, A^3 is cycloalkyl, and Group G^1 is R^0, halogen, —OH, —CO_2H, —CO_2R^0, —CO_2—R^{00}-(phenyl), —SO_2—R^{00}—CO_2R^0, —R^{00}—CO_2H, —R^{00}—CO_2R^0, and phenyl.

(5-7) The compound of formula (I) or a salt thereof, wherein R^4 is A^3, A^3 is cycloalkyl, and Group G^1 is halogen and R^0.

(5-8) The compound of formula (I) or a salt thereof, wherein R^4 is —Y-A^2, Y is C_{1-10} alkylene, C_{2-10} alkenylene, or —SO_2—R^{00}—, Group G^2 is —CO_2H, —CO_2R^0, —OH, and —OR^0, and A^2 is H, —OH or —$CONH_2$, or phenyl, pyridyl, pyrimidinyl, triazinyl, pyrrolyl, pyrazolyl, thienyl, furyl, thiazolyl, oxazolyl, isoxazolyl, isoxadiazolyl, tetrazolyl, quinoxazolyl, piperidyl, piperazyl, morpholyl, thiomorpholyl, tetrahydropyranyl, tetrahydrothiopyranyl, quinuclidyl, or monocyclic C_{3-8} cycloalkyl, each of which is optionally substituted with at least one group selected from the group consisting of —OH, oxo, —OR^0, —O—R^{00}—CO_2R^0, —O—R^{00}—CO_2H, —CO—R^0, —NH_2, —CO_2H, —CO_2R^0, —SO_2—R^0, R^{00}—CO_2H, halogen, phenyl, morpholyl, 4-carboxypiperidyl, 4-alkoxycarbonylpiperidyl, 3-alkoxycarbonylpiperidyl, 3-carboxypiperidyl, R^0, and halogeno-lower alkyl.

(5-9) The compound of formula (I) or a salt thereof, which is selected from the group consisting of the following (5-10), (5-11), and (5-13).

(5-10) The compound of formula (I) or a salt thereof, wherein R^4 is A^3, A^3 is pyrrolidyl optionally substituted with at least one group selected from Group G^1, piperidyl optionally substituted with at least one group selected from Group G^1, or piperazyl optionally substituted with at least one group selected from Group G^1, and Group G^1 is R^0.

(5-11) The compound of formula (I) or a salt thereof, wherein R^4 is A^3, A^3 is monocyclic C_{3-8} cycloalkyl optionally substituted with at least one group selected from Group G^1, or indanyl optionally substituted with at least one group selected from Group G^1, and Group G^1 is halogen, —CO_2H, and —OH.

(5-12-1) The compound of formula (I) or a salt thereof, wherein R^4 is A^3, A^3 is monocyclic C_{3-8} cycloalkyl or indanyl, each optionally substituted with at least one group selected from Group G^1, and Group G^1 is —CO_2H, —OH, halogen, and R^0.

(5-12-2) The compound of formula (I) or a salt thereof, wherein R^4 is A^3, A^3 is indanyl optionally substituted with at least one group selected from Group G^1, and Group G^1 is halogen, —CO_2H, —CO_2R^0, —R^{00}—OH, and —OH.

(5-12-3) The compound of formula (I) or a salt thereof, wherein R^4 is A^3, A^3 is tetrahydronaphthyl optionally substituted with at least one group selected from Group G^1, and Group G^1 is —CO_2H and —CO_2R^0.

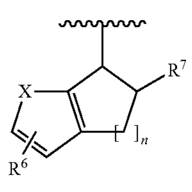
(5-12-4) The compound of formula (I) or a salt thereof, wherein R^4 is A^3, A^3 is dihydrobenzofuranyl optionally substituted with at least one group selected from Group G^1, and Group G^1 is —CO_2H and —CO_2R^0.

(5-13) The compound of formula (I) or a salt thereof, wherein R^4 is Y is C_{1-10} alkylene optionally substituted with at least one group selected from Group G^2, or C_{2-10} alkenylene optionally substituted with at least one group selected from Group G^2, Group G^2 is —CO_2H, —CO_2R^0, and —OH, and A^2 is H, or phenyl optionally substituted with at least one group selected from the group consisting of R^0, halogen, and —CO_2H.

(5-14) The compound of formula (I) or a salt thereof, wherein R^4 is A^3, A^3 is a group represented by the following formula (A) or (B):

[Chem. 9]

(A)



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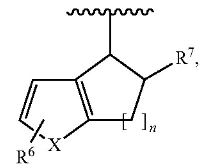
(B)



R^6 is H, halogen, or lower alkyl, R^7 is —CO_2H, —CO_2R^0, —CN, —NO_2, —SO_3H, or —SO_3R^0, X is NH, NR^0, O, S, or —HC═CH—, and n is 1 or 2.

(5-14-1) The compound or a salt thereof according to (5-14), wherein R^4 is A^3 and A^3 is a group represented by the formula (A).

(5-14-2) The compound or a salt thereof according to (5-14), wherein R^4 is A^3 and A^3 is a group represented by the formula (B).

(5-14-3) The compound or a salt thereof according to (5-14), wherein R^4 is A^3, A^3 is a group represented by the formula (A) or the formula (B), and X is —HC═CH—.

(5-14-4) The compound or a salt thereof according to (5-14), wherein R^4 is A^3, A^3 is a group represented by the formula (A), and X is S.

(5-14-5) The compound or a salt thereof according to (5-14), wherein R^4 is A^3, A^3 is a group represented by the formula (B), and X is S.

(5-14-6) The compound or a salt thereof according to (5-14), wherein R^4 is A^3, A^3 is a group represented by the formula (A) or the formula (B), X is —HC═CH—, and n is 1.

(5-14-7) The compound or a salt thereof according to (5-14), wherein R^4 is A^3, A^3 is a group represented by the formula (A) or the formula (B), X is —HC═CH—, and n is 2.

(5-14-8) The compound or a salt thereof according to (5-14), wherein R^4 is A^3, A^3 is a group represented by the formula (A) or the formula (B), X is —HC═CH—, and R^6 is H, F, or methyl, in another embodiment, R^6 is F or methyl, in still another embodiment, R^6 is H, in still another embodiment, R^6 is F, and in a further still another embodiment, R^6 is methyl.

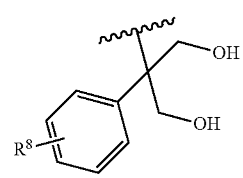
(5-14-9) The compound or a salt thereof according to (5-14), wherein R^4 is A^3, A^3 is a group represented by the formula (A) or the formula (B), X is —HC═CH—, and R^7 is —CO_2H or —CO_2R^0, in still another embodiment, R^7 is —CO_2H, and in a further still another embodiment, R^7 is —CO_2R^0.

(5-14-10) The compound or a salt thereof according to (5-14), wherein X is S or —HC═CH—.

(5-15) The compound of formula (I) or a salt thereof, wherein R^4 is —Y-A^2, —Y-A^2 is a group represented by the following formula (C) or (D):

[Chem. 10]

(C)



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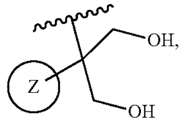
(D)



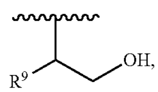
R^8 is H or lower alkyl, and Ring Z is unsubstituted pyridyl.

(5-16) The compound of formula (I) or a salt thereof, wherein R^4 is A^3, A^3 is 1,3-dioxane optionally substituted with at least one group selected from Group G^1, and Group G^1 is phenyl optionally substituted with R^0, R^0, and pyridyl.

(5-17) The compound of formula (I) or a salt thereof, wherein R^4 is —Y-A^2, —Y-A^2 is a group represented by the following formula (E):

[Chem. 11]

(E)

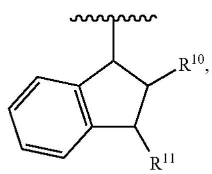


and R^9 is phenyl or lower alkyl.

(5-18) The compound of formula (I) or a salt thereof, wherein R^4 is A^3, A^3 is a group represented by the following formula (F):

[Chem. 12]

(F)

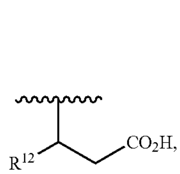


R^{10} is H or —OH, and R^{11} is H or —OH.

(5-19) The compound of formula (I) or a salt thereof, wherein R^4 is —Y-A^2, —Y-A^2 is a group represented by the following formula (G):

[Chem. 13]

(G)



and R^{12} is lower alkyl, cycloalkyl, or phenyl.

(6) The compound of the formula (I) or a salt thereof, wherein R^5 is each H; and in another embodiment, the compound of the formula (I) or a salt thereof, wherein any one of R^5's is H and another one is R^0.

(7) The compound or a salt thereof, including the combinations of two or more of the groups as described in (1) to (4), (5) to (5-5), (5-9) to (5-12), (5-13), and (6).

(7-1) The compound or a salt thereof, including the combinations of two or more of the groups as described in (1) to (4), (5-6), (5-7), (5-12-1), (5-14), and (5-14-1) to (5-14-9).

(7-2) The compound or a salt thereof, including the combinations of two or more of the groups as described in (1) to (4), (5-12-2) to (5-12-4), (5-15-1), and (5-16) to (5-18).

Examples of the compound that is a combination of two or more of the groups as described in (1) to (6) include the following compounds or salts thereof.

(8) The compound of the formula (I) or a salt thereof, wherein R^3 is H and R^5 is each H.

(9) The compound or a salt thereof according to (8), wherein R^2 is methyl and R^1 is H.

(10) The compound or a salt thereof according to (9), wherein A^1 is cyclohexyl or phenyl optionally substituted with one or more F atoms.

(11a) The compound or a salt thereof, which is selected from the compound group consisting of the following (11-1), (11-2), and (11-3).

(11-1) The compound or a salt thereof according to (10), wherein R^4 is A^3, A^3 is pyrrolidyl optionally substituted with at least one group selected from Group G^1 or piperidyl optionally substituted with at least one group selected from Group G^1, and Group G^1 is R^0.

(11-2) The compound or a salt thereof according to (10), wherein R^4 is A^3, A^3 is indanyl optionally substituted with at least one group selected from Group G^1, and Group G^1 is halogen, —CO_2H, and —OH.

(11-3) The compound or a salt thereof according to (10), wherein R^4 is —Y-A^2, Y is C_{1-10} alkylene optionally substituted with at least one group selected from Group G^2, Group G^2 is —CO_2H and —OH, and A^2 is H, or phenyl optionally substituted with —CO_2H.

(11b) The compound or a salt thereof, which is selected from the compound group consisting of (11-1), and the following (11-4) and (11-5).

(11-4) The compound or a salt thereof according to (10), wherein R^4 is A^3, A^3 is indanyl optionally substituted with at least one group selected from Group G^1, and Group G^1 is halogen, R^0, —CO_2H, and —OH.

(11-5) The compound or a salt thereof according to (10), wherein R^4 is —Y-A^2, Y is C_{1-10} alkylene optionally substituted with at least one group selected from Group G^2, Group G^2 is —CO_2H and —OH, and A^2 is H, or phenyl optionally substituted with at least one group selected from the group consisting of R^0, halogen, and —CO_2H.

(11-6) The compound or a salt thereof according to (10), wherein R^4 is —Y-A^2, —Y-A^2 is a group represented by the formula (C), and R^{8a} is H.

(11-7) The compound or a salt thereof according to (10), wherein R^4 is A^3, A^3 is cyclopentyl or piperidyl each of which is optionally substituted with at least one group selected from Group G^1, and Group G^1 is —OH, phenyl, and —SO_2—NH_2.

(11-8) The compound or a salt thereof according to (10), wherein R^4 is A^3, A^3 is indanyl optionally substituted with at least one group selected from Group G^1, and Group G^1 is —CO_2H and —OH.

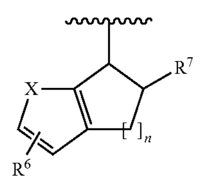
(11-9) The compound of formula (I) or a salt thereof, wherein A^1 is cyclohexyl, or phenyl optionally substituted with one or more F atom, R^1 is H, R^2 is R^0, R^3 is H, R^5 is H, R^4 is —Y-A^2 or A^3, Y is C_{1-10} alkylene optionally substituted with at least one group selected from Group G^2, Group G^2 is —CO_2H and —OH, A^2 is H, cycloalkyl, pyridyl, or phenyl optionally substituted with a group selected from lower alkyl and —CO_2H, A^3 is cycloalkyl selected from the group consisting of cyclopentyl, indanyl, dihydrocyclopentathienyl, dihydrocyclopentafuranyl, and dihydrocyclopentapyrrolyl, the above cycloalkyl is optionally substituted with at least one group selected from Group G^1, or piperidyl or pyrrolidyl each optionally substituted with at least one group selected from Group G^1, and Group G^1 is R^0, halogen, —CO_2H, —OH, —CO_2R^0, —CN, —NO_2, phenyl, —SO_2—NH_2, —SO_3H, and —SO_3R^0.

(12) The compound of formula (I) or a salt thereof, wherein A^1 is cycloalkyl optionally substituted or aryl optionally substituted, R^1 is H, R^0, halogen, —CN, —CO_2H, —CO_2R^0, or —R^{00}—OH, R^2 is H, R^0, or halogeno-lower alkyl, R^3 is H, R^0, —R^{00}—CO_2H, or —R^{00}—CO_2R^0, R^4 is A^3, A^3 is a group represented by the formula (A) or (B), R^6 is H, halogen, or lower alkyl, R^7 is —CO_2H, —CO_2R^0, —CN, —NO_2, —SO_3H, or —SO_3R^0, X is NH, NR^0, O, S, or —HC═CH—, and n is 1 or 2.

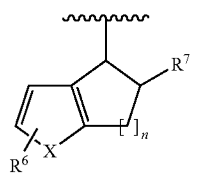
(12-1) The compound or a salt thereof as described in (11-9), wherein A^1 is cyclohexyl, 2-fluorophenyl, 2,3-difluorophenyl, 2,6-difluorophenyl, or 2,3,6-trifluorophenyl, R^4 is a group represented by any one of the following formulae (A), (B), (C), (D), (E), (F), or (G):

[Chem. 14]

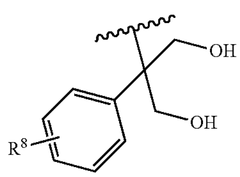
(A)



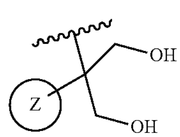
(B)



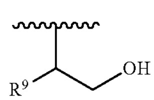
(C)



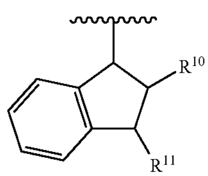
(D)



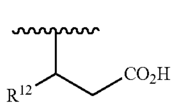
(E)



(F)



(G)



wherein R^6 is H, halogen, or R^0, R^7 is —CO_2H, —CO_2R^0, —CN, —NO_2, —SO_3H, or —SO_3R^0, X is NH, NR^0, O, S, or —HC═CH—, n is 1 or 2, R^8 is H or lower alkyl, Z is pyridyl, R^9 is phenyl or lower alkyl, R^{10} is H or —OH, R^{11} is H or —OH, and R^{12} is lower alkyl, cycloalkyl, or phenyl.

(12-2) The compound of formula (I) or a salt thereof, wherein A^1 is cyclohexyl, 2-fluorophenyl, 2,3-difluorophenyl, 2,6-difluorophenyl, or 2,3,6-trifluorophenyl, R^1 is H, R^2 is R^0, R^3 is H, R^4 is —Y-A^2, Y is C_{1-10} alkylene optionally substituted with at least one group selected from Group G^2, Group G^2 is —CO_2H and —OH, and A^2 is H, or phenyl optionally substituted with —CO_2H.

(12-2-1) The compound or a salt thereof as described in (12-1), wherein R^2 is methyl and R^4 is a group represented by the formula (C) or (D).

(12-2-2) The compound or a salt thereof as described in (12-1), wherein R^2 is methyl and R^4 is a group represented by the formula (E).

(12-3) The compound of formula (I) or a salt thereof, wherein A^1 is cyclohexyl, 2-fluorophenyl, 2,3-difluorophenyl, 2,6-difluorophenyl, or 2,3,6-trifluorophenyl, R^1 is H, R^2 is R^0, R^3 is H, R^4 is A^3, A^3 is indanyl optionally substituted with at least one group selected from Group G^1, and Group G^1 is halogen, —CO_2H, and —OH.

(12-4) The compound of formula (I) or a salt thereof, wherein A^1 is cyclohexyl, 2-fluorophenyl, 2,3-difluorophenyl, 2,6-difluorophenyl, or 2,3,6-trifluorophenyl, R^1 is H, R^2 is R^0, R^3 is H, R^4 is A^3, A^3 is cyclopentyl or piperidyl, and Group G^1 is —OH, phenyl, and —SO_2—NH_2.

(12-5) The compound of formula (I) or a salt thereof, wherein A^1 is cyclohexyl, 2-fluorophenyl, 2,3-difluorophenyl, 2,6-difluorophenyl, or 2,3,6-trifluorophenyl, R^1 is H, R^2 is R^0, R^3 is H, R^4 is A^3, R^5 is H, A^3 is indanyl optionally substituted with at least one group selected from Group G^1, and Group G^1 is —CO_2H and —OH.

(13) The compound or a salt thereof as described in (12-1), wherein A^1 is 2,6-difluorophenyl, R^2 is methyl, R^4 is A^3, A^3 is a group represented by the formula (A) or the formula (B), X is —HC═CH—, n is 1, R^5 is each H, R^6 is F or methyl, and R^7 is —CO_2H.

(14) The compound or a salt thereof as described in (13), wherein R^6 is F.

(15) The compound or a salt thereof as described in (13), wherein R^6 is methyl.

(16) The compound or a salt thereof as described in (12), wherein A^1 is cycloalkyl, R^1 is H, R^2 is methyl, R^3 is H, X is —HC═CH—, n is 1, R^5 is each H, R^6 is F or methyl, and R^7 is —CO_2H.

(17) The compound or a salt thereof as described in (16), wherein R^6 is F.

(17-1) The compound or a salt thereof as described in (12-1), wherein A^1 is cyclohexyl or 2,6-difluorophenyl, R^2 is methyl, R^4 is A^3, A^3 is a group represented by the formula (A) or the formula (B), X is —HC═CH—, n is 1, R^5 is each H, R^6 is H, and R^7 is —CO_2H.

(18) The compound or a salt thereof as described in (16), wherein R^6 is methyl.

(19) The compound of formula (I) or a salt thereof, wherein A^1 is 2,3,6-trifluorophenyl, R^1 is H, R^2 is methyl, R^3 is H, R^4 is A^3, A^3 is a group represented by the formula (A) or the formula (B), X is —HC═CH—, n is 1, R^5 is each H, R^6 is H, and R^7 is —CO_2H.

(20) The compound of formula (I) or a salt thereof, wherein A^1 is cycloalkyl, R^1 is H, R^2 is methyl, R^3 is H, R^4 is A^3, A^3 is a group represented by the formula (A) or the formula (B), X is —HC═CH—, n is 1, R^5 is each H, R^6 is H, and R^7 is —CO_2H.

(21) The compound of formula (I) or a salt thereof, wherein A^1 is 2,6-difluorophenyl, R^1 is H, R^2 is methyl, R^3

is H, R^4 is A^3, A^3 is a group represented by the formula (A) or the formula (B), X is —HC═CH—, n is 1, R^5 is each H, R^6 is H, and R^7 is —CO_2H.

(22) The compound or a salt thereof as described in (12-1), wherein R^2 is methyl and R^4 is a group represented by the formula (F).

(23) The compound of or a salt thereof as described in (12-1), wherein R^2 is methyl and R^4 is a group represented by the formula (G).

Examples of the specific compounds included in the present invention are the following compounds.

Compounds or salts thereof selected from the group consisting of:

(3S)-3-({[8-(cyclohexylmethoxy)-2-methylimidazo[1,2-a]pyridin-3-yl]carbonyl}amino)-3-phenylpropanoic acid,

(1S,2R)-1-[({8-[(2,6-difluorobenzyl)oxy]-2-methylimidazo[1,2-a]pyridin-3-yl}carbonyl)amino]indane-2-carboxylic acid,

(1S,2R)-1-({[8-(cyclohexylmethoxy)-2-methylimidazo[1,2-a]pyridin-3-yl]carbonyl}amino)indane-2-carboxylic acid,

(1R,2S)-1-({[8-(cyclohexylmethoxy)-2-methylimidazo[1,2-a]pyridin-3-yl]carbonyl}amino)indane-2-carboxylic acid,

8-[(2,6-difluorobenzyl)oxy]-N-(1,3-dihydroxy-2-phenylpropan-2-yl)-2-methylimidazo[1,2-a]pyridine-3-carboxamide,

(1S,2R)-1-[({8-[(2,6-difluorobenzyl)oxy]-2-methylimidazo[1,2-a]pyridin-3-yl}carbonyl)amino]-7-fluoroindane-2-carboxylic acid,

(1S,2R)-1-[({8-[(2,6-difluorobenzyl)oxy]-2-methylimidazo[1,2-a]pyridin-3-yl}carbonyl)amino]-4-methylindane-2-carboxylic acid,

(1S,2R)-1-({[8-(cyclohexylmethoxy)-2-methylimidazo[1,2-a]pyridin-3-yl]carbonyl}amino)-5-fluoroindane-2-carboxylic acid,

(1S,2R)-1-({[8-(cyclohexylmethoxy)-2-methylimidazo[1,2-a]pyridin-3-yl]carbonyl}amino)-7-fluoroindane-2-carboxylic acid,

(1R,2S)-1-({[8-(cyclohexylmethoxy)-2-methylimidazo[1,2-a]pyridin-3-yl]carbonyl}amino)-7-fluoroindane-2-carboxylic acid,

(1S,2R)-1-({[8-(cyclohexylmethoxy)-2-methylimidazo[1,2-a]pyridin-3-yl]carbonyl}amino)-4-methylindane-2-carboxylic acid,

(1S,2R)-1-[({2-methyl-8-[(2,3,6-trifluorobenzyl)oxy]imidazo[1,2-a]pyridin-3-yl}carbonyl)amino]indane-2-carboxylic acid,

8-[(2,6-difluorobenzyl)oxy]-N-[(1R)-2-hydroxy-1-phenylethyl]-2-methylimidazo[1,2-a]pyridine-3-carboxamide,

8-[(2,6-difluorobenzyl)oxy-N-[(1R,2R)-2-hydroxy-2,3-dihydro-1H-inden-1-yl]-2-methylimidazo[1,2-a]pyridine-3-carboxamide,

8-[(2,3-difluorobenzyl)oxy]-N-(1,3-dihydroxy-2-phenylpropan-2-yl)-2-methylimidazo[1,2-a]pyridine-3-carboxamide,

8-[(2,6-difluorobenzyl)oxy]-N-[1,3-dihydroxy-2-(pyridin-2-yl)propan-2-yl]-2-methylimidazo[1,2-a]pyridine-3-carboxamide,

8-(cyclohexylmethoxy)-N-[(1R)-2-hydroxy-1-phenylethyl]-2-methylimidazo[1,2-a]pyridine-3-carboxamide,

8-[(2,6-difluorobenzyl)oxy]-N-[(2R)-1-hydroxypropan-2-yl]-2-methylimidazo[1,2-a]pyridine-3-carboxamide,

8-[(2,6-difluorobenzyl)oxy]-N-[(2R)-1-hydroxy-3-methylbutan-2-yl]-2-methylimidazo[1,2-a]pyridine-3-carboxamide, and

N-(1,3-dihydroxy-2-phenylpropan-2-yl)-8-[(2-fluorobenzyl)oxy]-2-methylimidazo[1,2-a]pyridine-3-carboxamide.

Furthermore, the following compounds are examples of specific compounds included in the present invention.

Compounds or salts thereof selected from the group consisting of:

8-[(2,6-difluorobenzyl)oxy]-N-[(1R,2S,3S)-2,3-dihydroxy-2,3-dihydro-1H-inden-1-yl]-2-methylimidazo[1,2-a]pyridine-3-carboxamide,

8-[(2,3-difluorobenzyl)oxy]-N-[(1R,2S,3S)-2,3-dihydroxy-2,3-dihydro-1H-inden-1-yl]-2-methylimidazo[1,2-a]pyridine-3-carboxamide, and

N-[(1R,2S,3S)-2,3-dihydroxy-2,3-dihydro-1H-inden-1-yl]-8-[(2-fluorobenzyl)oxy]-2-methylimidazo[1,2-a]pyridine-3-carboxamide.

Still further, the following compounds are examples of specific compounds included in the present invention.

Compounds or salts thereof selected from the group consisting of:

8-[(2,6-difluorobenzyl)oxy]-N-[(1R,2S,3R)-2,3-dihydroxy-2,3-dihydro-1H-inden-1-yl]-2-methylimidazo[1,2-a]pyridine-3-carboxamide,

8-[(2,3-difluorobenzyl)oxy]-N-[(1R,2S,3R)-2,3-dihydroxy-2,3-dihydro-1H-inden-1-yl]-2-methylimidazo[1,2-a]pyridine-3-carboxamide, and

N-[(1R,2S,3R)-2,3-dihydroxy-2,3-dihydro-1H-inden-1-yl]-8-[(2-fluorobenzyl)oxy]-2-methylimidazo[1,2-a]pyridine-3-carboxamide.

Still further, the following compounds are examples of specific compounds included in the present invention.

Compounds or pharmaceutically acceptable salts thereof selected from the group consisting of:

8-[(2,6-difluorobenzyl)oxy]-N-[(1r,3R,4S)-3,4-dihydroxy-1-phenylcyclopentyl]-2-methylimidazo[1,2-a]pyridine-3-carboxamide and

8-[(2,6-difluorobenzyl)oxy]-N-[(1s,3R,4S)-3,4-dihydroxy-1-phenylcyclopentyl]-2-methylimidazo[1,2-a]pyridine-3-carboxamide.

Still further, the following compounds are examples of specific compounds included in the present invention.

Compounds or salts thereof selected from the group consisting of:

8-(cyclohexylmethoxy)-2-methyl-N-[(3S)-1-methylpiperidin-3-yl]imidazo[1,2-a]pyridine-3-carboxamide,

(3R)-3-({[8-(cyclohexylmethoxy)-2-methylimidazo[1,2-a]pyridin-3-yl]carbonyl}amino)-5-methylhexanoic acid,

8-(cyclohexylmethoxy)-N-(1,3-dihydroxypropan-2-yl)-2-methylimidazo[1,2-a]pyridine-3-carboxamide,

8-(cyclohexylmethoxy)-2-methyl-N-[(3S)-1-methylpyrrolidin-3-yl]imidazo[1,2-a]pyridine-3-carboxamide,

3-[(1S)-1-({[8-(cyclohexylmethoxy)-2-methylimidazo[1,2-a]pyridin-3-yl]carbonyl}amino)ethyl]benzoic acid,

8-[(2,6-difluorobenzyl)oxy]-N-(1-hydroxy-2-methylpropan-2-yl)-2-methylimidazo[1,2-a]pyridine-3-carboxamide,

8-[(2,6-difluorobenzyl)oxy]-N-[(1R,2S)-2,3-dihydroxy-1-phenylpropyl]-2-methylimidazo[1,2-a]pyridine-3-carboxamide,

(3R)-4-cyclobutyl-3-({[8-(cyclohexylmethoxy)-2-methylimidazo[1,2-a]pyridin-3-yl]carbonyl}amino)butanoic acid,

8-[(2,6-difluorobenzyl)oxy]-2-methyl-N-[(3S)-1-sulfamoylpiperidin-3-yl]imidazo[1,2-a]pyridine-3-carboxamide, and

8-[(2,6-difluorobenzyl)oxy]-2-methyl-N-[(3S)-piperidin-3-yl]imidazo[1,2-a]pyridine-3-carboxamide.

The compound of formula (I) may exist in the form of tautomers or geometrical isomers depending on the kind of substituents. In the present specification, the compound of formula (I) shall be described in only one isomer form, yet the present invention includes any other isomers, in their isolated form, or as mixtures thereof.

In addition, the compound of formula (I) may have asymmetric carbon atoms or axial asymmetries in some cases, and therefore, optical isomers may exist based thereon. The present invention includes both isolated forms of optical isomers of the compound of formula (I) or any mixture thereof.

Moreover, the present invention also includes a pharmaceutically acceptable prodrugs of the compound of formula (I). Pharmaceutically acceptable prodrugs are compounds having groups that can be converted into an amino group, a hydroxyl group, a carboxyl group, or the like through solvolysis or under physiological conditions. Examples of the group forming the prodrug include the groups described in Prog. Med., 5, 2157-2161 (1985) and "Pharmaceutical Research and Development" (Hirokawa Publishing Company, 1990), Vol. 7, Drug Design, 163-198.

Furthermore, salts of the compound of formula (I) are pharmaceutically acceptable salts of the compound of formula (I) and may form an acid addition salt or a salt with a base depending on the kind of substituents. Specific examples thereof include acid addition salts with inorganic acids such as hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, nitric acid, phosphoric acid, and the like, and with organic acids such as formic acid, acetic acid, propionic acid, oxalic acid, malonic acid, succinic acid, fumaric acid, maleic acid, lactic acid, malic acid, mandelic acid, tartaric acid, dibenzoyltartaric acid, ditolyltartaric acid, citric acid, methanesulfonic acid, ethanesulfonic acid, benzenesulfonic acid, p-toluenesulfonic acid, aspartic acid, glutamic acid, and the like, and salts with inorganic bases such as sodium, potassium, magnesium, calcium, aluminum, and the like or organic bases such as methylamine, ethylamine, ethanolamine, lysine, ornithine, and the like, salts with various amino acids or amino acid derivatives such as acetylleucine and the like, ammonium salts, etc.

In addition, the present invention also includes various hydrates or solvates, and polymorphic crystalline substances of the compound of formula (I) or d a salt thereof. In addition, the present invention also includes compounds labeled with various radioactive or non-radioactive isotopes.

(Preparation Methods)

The compound of formula (I) and salts thereof can be prepared using the characteristics based on the basic structure or the type of substituents thereof and by applying various known synthesis methods. During the preparation, replacing the relevant functional group with a suitable protective group (a group that can be easily converted into the relevant functional group) at the stage from starting material to an intermediate may be effective depending on the type of the functional group in the production technology in some cases. The protective group for such a functional group may include, for example, the protective groups described in "Greene's Protective Groups in Organic Synthesis (4th edition, 2006)", P. G. M. Wuts and T. W. Greene, and one of these may be selected and used as necessary depending on the reaction conditions. In this kind of method, a desired compound can be obtained by introducing the protective group, by carrying out the reaction and by eliminating the protective group as necessary.

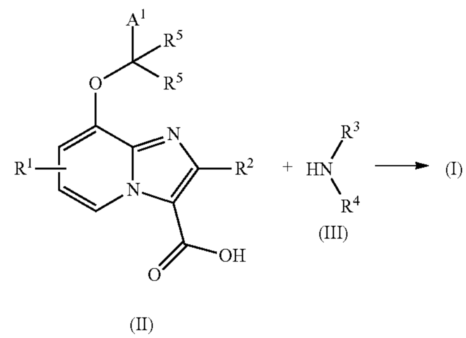
In addition, prodrugs of the compound of formula (I) can be prepared by introducing a specific group or by carrying out the reaction using the obtained compound of formula (I) at the stage from a starting material to an intermediate, just as in the case of the above-mentioned protective group. The reaction can be carried out using methods known to a person skilled in the art, such as ordinary esterification, amidation, dehydration, and the like.

Hereinbelow, representative preparation methods for the compound of formula (I) will be described. Each production process may also be carried out with reference to the References appended in the present description. Further, the preparation methods of the present invention are not limited to the examples as shown below.

(General Production Processes)

(Production Process 1)

[Chem. 15]



The compound of formula (I) can be prepared by reacting compound (II) with compound (III).

In this production process, compound (II) and compound (III) are used in equivalent amounts, or either thereof in an excess amount, and their mixture is stirred in a range of from cooling to heating, preferably at a temperature from −20° C. to 60° C., usually for about 0.1 hours to 5 days, in a solvent which is inert to the reaction, in the presence of a condensing agent. The solvent hereinused is not particularly limited, but examples thereof include aromatic hydrocarbons such as benzene, toluene, xylene, and the like, halogenated hydrocarbons such as dichloromethane, 1,2-dichloroethane, chloroform, and the like, ethers such as diethyl ether, tetrahydrofuran (THF), dioxane, dimethoxyethane, and the like, N,N-dimethylformamide (DMF), dimethylsulfoxide (DMSO), ethyl acetate, acetonitrile, or water, and any mixture thereof. Examples of condensing agents include, but are not limited to, 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (WSC), dicyclohexylcarbodiimide (DCC), 1,1'-carbonyldiimidazole (CDI), diphenylphosphoryl azide (DPPA), and phosphorous oxychloride. In some cases, it may be preferable for the reaction to use an additive (for example, 1-hydroxybenzotriazole (HOBt)). It is in some cases advantageous for smooth progress of the reaction to carry out the reaction in the presence of organic bases such as triethylamine (TEA), N,N-diisopropylethylamine (DIPEA), N-methylmorpholine (NMM), and the like, or inorganic bases such as potassium carbonate, sodium carbonate, potassium hydroxide, and the like.

Furthermore, it is also possible to use a method in which compound (II) is converted to a reactive derivative and afterward reacted with compound (III). Examples of reactive derivatives of compound (II) include acid halides that can be obtained by the reaction with a halogenating agent such as phosphorus oxychloride, thionyl chloride, and the like, mixed acid anhydrides obtained by the reaction with isobutyl chloroformate or the like, active esters obtained by condensation with 1-hydroxybenzotriazole or the like, etc. The reaction of these reactive derivatives with compound (III) can be carried out in a range of from cooling to heating, and preferably from −20° C. to 60° C., in a solvent which is inert to the reaction, such as halogenated hydrocarbons, aromatic hydrocarbons, ethers, and the like. For this reaction, for example, the following references may be referred to.

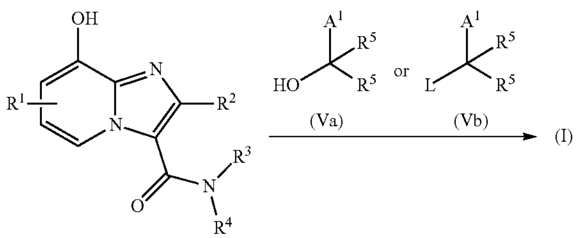
"Organic Functional Group Preparations", S. R. Sandler and W. Karo, 2nd edition, Vol. 1, Academic Press Inc., 1991

The Chemical Society of Japan, "Courses in Experimental Chemistry (5th edition)" Vol. 16 (2005) (Maruzen)

In addition, further compounds of formula (I) can also be prepared from the compound of formula (I) prepared by this Production Process (for details, Examples as described later may be referred to).

(Production Process 2)

[Chem. 16]



(IV)

(wherein L represents a leaving group, for example, halogen).

Furthermore, the compound of formula (I) can be prepared by reacting compound (IV) with compound (Va) or compound (Vb).

Examples of the preparation method using compound (Va) include methods in which known diazocarboxylic esters or diazocarboxylic amides are used in combination with phosphines, (tributylphosphoraniliden)acetonitrile (Tsunoda reagent), or the like. These are the so-called Mitsunobu reaction, or any modified method thereof. These reactions are known to the skilled in the art.

In this reaction, compound (IV) and compound (Va) are used in equivalent amounts, or in an excess amount for either thereof, and their mixture is stirred in a range of from cooling to heating under refluxing, preferably at a temperature from 0° C. to 150° C., usually for about 0.1 hours to 5 days, in a solvent which is inert to the reaction. The solvent as used herein is not particularly limited, but examples thereof include, aromatic hydrocarbons, ethers, halogenated hydrocarbons, DMF, DMSO, ethyl acetate, acetonitrile, and a mixture thereof.

For this reaction, for example, the following references may be referred to.

Mitsunobu, O.; Synthesis (1981), 1

Tsunoda, T. et al., Tetrahedron Letters (1995) 36, 2529, ibid, (1996) 37, 2463

On the other hand, when compound (Vb) is used, compound (IV) and compound (Vb) are used in equivalent amounts, or in an excess amount for either thereof, and their mixture is stirred in a range of from cooling to heating and refluxing, preferably at a temperature from 0° C. to 80° C., usually for about 0.1 hours to 5 days, in a solvent which is inert to the reaction, in the presence of a base. The solvent as used herein is not particularly limited, but examples thereof include aromatic hydrocarbons such as benzene, toluene, xylene, and the like, ethers such as diethyl ether, tetrahydrofuran, dioxane, dimethoxyethane, and the like, halogenated hydrocarbons such as dichloromethane, 1,2-dichloroethane, chloroform, and the like, N,N-dimethylformamide, dimethylsulfoxide, ethyl acetate, acetonitrile, and any mixture thereof. Examples of bases include organic bases such as triethylamine, diisopropylethylamine, 1,8-diazabicyclo[5.4.0]-7-undecene, n-butyllithium, and the like, and inorganic bases such as sodium carbonate, potassium carbonate, sodium hydride, potassium tert-butoxide, and the like. It may be advantageous in some cases to carry out the reaction in the presence of a phase transfer catalyst such as tetra-n-butylammonium chloride, and the like.

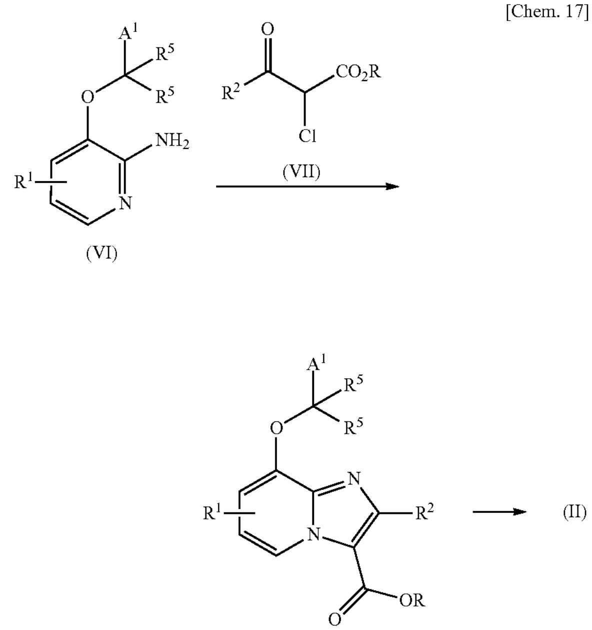
For this reaction, for example, the following references may be referred to.

"Organic Functional Group Preparations", S. R. Sandler and W. Karo, 2nd edition, Vol. 1, Academic Press Inc., 1991

The Chemical Society of Japan, "Courses in Experimental Chemistry (5th edition)" Vol. 14 (2005) (Maruzen)

(Starting Material Synthesis)

[Chem. 17]



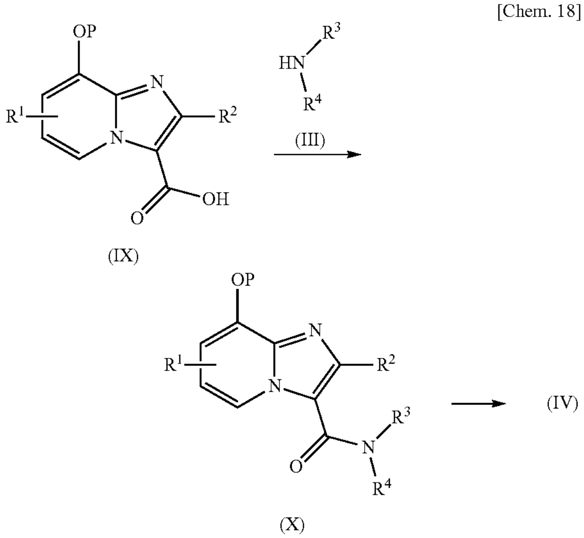
(VIII)

(wherein R is lower alkyl or the like, for example, methyl or ethyl).

The starting material compound (II) can be prepared by hydrolyzing compound (VIII) which is prepared by reacting compound (VI) with compound (VII).

The reaction for preparing the compound (VIII) can be carried out with the same reaction solvent and temperature as in Production Process 1 (for details, Examples as described later may be referred to).

[Chem. 18]



(wherein P is a protective group, for example, benzyl).

The starting material compound (IV) can be prepared by reacting compound (IX) and compound (III) to prepare compound (X), which is thus subjected to deprotection. The reaction of compound (IX) with compound (III) can be carried out in the same way as in Production Process 1. Further, the deprotection can be carried out by known methods or those obvious to the skilled in the art.

The compounds of formula (I) can be isolated and purified as free compounds, salts, hydrates, solvates, or polymorphic crystalline substances thereof. Salts of the compound of formula (I) can be prepared by conventional salt forming reactions.

Isolation and purification are carried out by employing ordinary chemical operations such as extraction, fractional crystallization, fractional chromatography, and the like.

Various isomers can be prepared by selecting appropriate starting compounds or by separation using the difference in physicochemical properties between the isomers. For example, optical isomers can be obtained by means of a general optical resolution method for racemic products (for example, fractional crystallization for inducing diastereomer salts with optically active bases or acids, chromatography using a chiral column or the like, and others), and further, the isomers can also be prepared from an appropriate optically active starting compound.

TEST EXAMPLES

Pharmacological activities of the compound of formula (I) were confirmed in the following tests.

Test Example 1

Measurement of sGC Activation (Enzyme)

The activity of sGC was evaluated by measuring the amount of a cyclic guanosine monophosphate (cGMP) which is produced by human purified sGC.

A test compound was dissolved in DMSO and diluted 20-fold with ultrapure water. 2 μL of the diluted test compound solution (maximum concentration 100 μM), 2 μL of a substrate solution [0.5 μM TEBA, 0.03 μM dithiothreitol, 0.01 μM GTP, 0.04 μM $MgCl_2$, and 0.03 μM sodium

nitroprusside (SNP)], and 6 μL of a human enzyme suspension were added to 384-well plates (manufactured by Greiner Bio-One), and incubated at room temperature for one hour. The quantitative determination of cGMP is using HTRF which based on the competition between sample cGMP and fluorescent dye labeled cGMP for binding to a cGMP-specific antibody.

The test results of some Example compounds that are the compounds of the formula (I) of the present invention are shown below. The sGC activation of the test compound was calculated by taking the activation when the compound was not added as 100%. As compared with the activation when the compound was not added, it was recognized that a compound having a sGC activation of more than 300% has sGC activation. In addition, in Tables, Ex represents Example number in which the test compound is described and the sGC activation [%] represents sGC activation (%).

Furthermore, the EC_{50} [μM] value was calculated as another parameter for expressing sGC activation. This parameter indicates the concentration of the evaluated compound giving 50% of a maximum activation, which is calculated based on the maximum activation that compound of Example 102 is added, which is taken as 100%. In this connection, when a known sGC activator, YC-1 (Lificiguat, [5-(1-benzyl-1H-indazol-3-yl)-2-furyl]methanol), was evaluated according to the above Test Example 1, its maximum activation was 52% of the maximum activation for compound of Example 102. Further, "–" means no evaluation.

TABLE 1

Ex	sGC activation [%]	EC_{50} [μM]
Ex 12	—	3.0
Ex 102	—	2.8
Ex 104	>1000	—
Ex 110	>1000	—
Ex 119	—	2.9
Ex 126	—	11
Ex 179	—	2.7
Ex 205	>1000	—
Ex 244	>1000	—
Ex 226	>1000	6.7
Ex 247	—	2.4
Ex 251	>1000	6.1
Ex 259	>1000	—
Ex 321	>1000	4.5
Ex 323	—	13
Ex 341	980	6.9
Ex 424	>1000	2.4
Ex 430	—	2.6
Ex 434	—	7.3
Ex 436	>1000	—
Ex 633	830	—
Ex 693	>1000	17
Ex 695	>1000	—
Ex 698	>1000	19
Ex 699	>1000	15
Ex 702	>1000	6.2
Ex 704	>1000	11
Ex 705	—	11
Ex 706	>1000	4.7
Ex 759	—	2.2
Ex 760	—	5.9
Ex 766	—	17
Ex 767	—	3.0
Ex 772	—	5.4
Ex 776	—	15
Ex 778	—	6.3
Ex 797	—	8.9
Ex 798	—	8.6
Ex 822	—	5.6
Ex 828	—	7.6

TABLE 1-continued

Ex	sGC activation [%]	EC_{50} [μM]
Ex 829	—	2.7
Ex 834	—	4.1

Test Example 2

Blood Flow Increasing In Vivo

The hind limb blood flow in rats anesthetized with pentobarbital was measured by the following test method.

Wistar male rats were used. An administration liquid was prepared by adding N,N-dimethyl formamide, Polyethylene Glycol 400, TWEEN 80, a 0.5% methyl cellulose aqueous solution, a 0.5 M aqueous sodium bicarbonate solution, and 0.1 M hydrochloric acid to the test compound and dissolving the test compound in an appropriate manner depending on the compound. Thus prepared administration liquid was orally administered, and 2 hours later, the hind limb blood flow was measured using a laser blood flow imaging device (PIM II Integral) under anesthesia with intraperitoneal administration of 60 mg/kg of pentobarbital.

The compounds of Examples 244, 259, and 341 of the present invention each exhibited a blood flow increasing effect at a dose of 30 mg/kg. Further, the compounds of Examples 12, 102, 119, 179, 247, 251, 321, 424, 430, 693, 698, 699, 702, 704, 706, 759, 760, 767, and 834 each exhibited a blood flow increasing effect at a dose of 10 mg/kg.

Test Example 3

Measurement of Antihypertensive Effect In Vivo

Wistar male rats were used. Three days prior to administration of a drug, a cannula (PE-50, Becton, Dickinson and Company, Japan) filled with heparin physiological saline (200 U/mL, Ajinomoto Pharmaceuticals Co., Ltd.) was inserted and placed in the common carotid artery under anesthesia with intraperitoneal administration of 60 mg/kg of pentobarbital. The other end of the cannula was exposed to the back neck through the subcutaneous. After the recovery period, the placed cannula was connected to a pressure transducer (Life Kit DTS DX-100, Nihon Kohden Corporation) to record the blood pressure waveform through a Polygraph (AP-641G, Nihon Kohden Co., Ltd.) and PowerLab (ML870 PowerLab8/30 (AD Instruments Japan)). The heart rate was calculated using a heart rate measuring unit (AT-601G, Nihon Kohden Co., Ltd.). After stabilization of the blood pressure, the drug was orally administered to measure the blood pressure and the heart rates. The test compounds were administered by appropriately adding N,N-dimethylformamide, Polyethylene Glycol 400, TWEEN 80, a 0.5% aqueous methylcellulose solution, and a 0.5 M aqueous sodium bicarbonate solution, and 0.1 M hydrochloric acid therein according to the compounds and dissolving it.

The results from the measurement according to Test Example 3 are shown below according to the following criteria with a maximum value of the mean blood pressure reduction. A: <20 mmHg, B: 20 to 40 mmHg, and C: >40 mmHg

TABLE 1-1

	Administration dose (mg/kg po)	Blood pressure reduction
Ex 180	30	B
Ex 422	30	C
Ex 431	10	B
Ex 434	30	C
Ex 827	10	B

In Test Examples 1 and 2 above, it was confirmed in several Example compounds of the present invention that they have sGC activation and blood flow improving action. Accordingly, the compound of formula (I) can be used for treating sGC-related cardiovascular diseases, in particular, peripheral arterial diseases, as well as intermittent claudication and critical limb ischemia caused by the aforesaid peripheral arterial diseases or the like.

In addition, in Test Example 3 above, it was confirmed that in several Example compounds of the present invention that they have antihypertensive effect. Accordingly, the compound of formula (I) can be used for treating hypertension, or the like.

Pharmaceutical compositions containing one or more kinds of compound of formula (I) or a salt thereof as an active ingredient can be prepared using excipients that are usually used in the art, that is, excipients for pharmaceutical preparation, carriers for pharmaceutical preparation, and the like according to the methods usually used.

Administration can be accomplished either by oral administration via tablets, pills, capsules, granules, powders, solutions, and the like, or parenteral administration, such as injections such as intraarticular, intravenous, and intramuscular injections, suppositories, ophthalmic solutions, eye ointments, transdermal solutions, ointments, transdermal patches, transmucosal solutions, transmucosal patches, inhalers, and the like.

Solid compositions for oral administration are used in the form of tablets, powders, granules, or the like. In such solid compositions, one or more active ingredient(s) are mixed with at least one inactive excipient. In a conventional method, the composition may contain inactive additives, such as lubricants, disintegrating agents, stabilizers, or solubilization assisting agents. If necessary, tablets or pills may be coated with sugar or s gastric- or enteric-soluble substances films.

Liquid compositions for oral administration comprises pharmaceutically acceptable emulsions, solutions, suspensions, syrups, elixirs, or the like, and also comprises generally used inert diluents, for example, purified water or ethanol (EtOH). In addition to the inert diluent, liquid compositions may also contain auxiliary agents, such as solubilization assisting agents, moistening agents, and suspending agents, sweeteners, flavors, aromatics, or antiseptics.

Injections for parenteral administration include sterile aqueous or non-aqueous solutions, suspensions, or emulsions. Aqueous solvents include, for example, distilled water for injection or physiological saline. Examples of non-aqueous solvents include alcohols such as ethanol. Such compositions may further contain tonicity agents, antiseptics, moistening agents, emulsifying agents, dispersing agents, stabilizers, or solubilization assisting agents. These are sterilized, for example, by filtration through bacteria retaining filter, blendings of bactericide, or irradiation. In addition, these can also be used by preparing sterile solid compositions, and dissolving or suspending in sterile water or sterile solvents for injection prior to its use.

Agents for external use includes ointments, plasters, creams, jellies, poultices, sprays, lotions, eye drops, eye ointments, and the like. The agents contain generally used ointment bases, lotion bases, aqueous or non-aqueous solutions, suspensions, emulsions, and the like.

As transmucosal agents such as inhalers, transnasal agents, and the like, those in the form of a solid, liquid, or semi-solid state are used, and can be prepared in accordance with conventionally known methods. For example, known excipients, and furthermore pH adjusting agents, antiseptics, surfactants, lubricants, stabilizers, thickening agents, or the like may be appropriately added thereto. For their administration, appropriate devices for inhalation or blowing can be used. For example, a compound may be administered alone or as a powder of formulated mixture, or as a solution or suspension in combination with pharmaceutically acceptable carriers, using a known device or sprayer, such as a measured administration inhalation device, and the like. Dry powder inhalers or the like may be for single or multiple administration use, and dry powder or powder-containing capsules may be used. Alternatively, these may be pressurized aerosol spray which uses appropriate ejection agents, for example, a suitable gas such as chlorofluoroalkane, hydrofluoroalkane, carbon dioxide, and the like.

For oral administration, daily dose is generally from about 0.001 to 100 mg/kg, preferably from 0.1 to 30 mg/kg, and more preferably from 0.1 to 10 mg/kg, per body weight, administered in one portion or in 2 to 4 separate portions. In the case of intravenous administration, daily dose is suitably administered from about 0.0001 to 10 mg/kg per body weight, once a day or two or more times a day. In addition, a transmucosal agent is administered at a dose from about 0.001 to 100 mg/kg per body weight, once a day or two or more times a day. Doses are appropriately determined according to the individual according to the symptoms, age, gender, and the like.

Although varying depending on administration routes, dosage forms, administration sites, or the types of excipients and additives, the pharmaceutical composition of the present invention contains 0.01 to 100% by weight, and in a certain embodiment, 0.01 to 50% by weight of one or more kinds of the compound of formula (I) or a salt thereof, as the active ingredient.

The compound of formula (I) can be used in combination with various therapeutic or prophylactic agents for the diseases for which the compound of formula (I) is considered to be effective, as described above. The combined preparation may be administered simultaneously, or separately and continuously, or at a desired time interval. The preparations to be administered simultaneously may be a mixture, or may be prepared individually.

EXAMPLES

Hereinbelow, the preparation methods for the compound of formula (I) will be described in more detail with reference to Examples. The present invention is not limited to the compounds described in Examples as described below. Further, the production processes for the starting compounds will be described in Preparation Examples. The compound of formula (I) is prepared by using a combination of the preparation methods or a method apparent to a person skilled in the art, in addition to Production Processes described in Examples.

Moreover, the following abbreviations may be used in some cases in Examples, Preparation Examples, and Tables as described later.

PEx: Preparation Example number, Ex: Example number, Str: Structural formula, Dat: Physicochemical data (ESI+: ESI-MS $[M+H]^+$ or ESI-MS $[M]^+$; ESI-: ESI-MS $[M-H]^-$; FAB+: FAB-MS $[M+H]^+$ or FAB-MS $[M]^+$; EI+: EI $[M]^+$; APCI/ESI+: APCI/ESI-MS $[M+H]^+$ or APCI/ESI-MS $[M]^+$ (APCI/ESI means simultaneous measurement of APCI and ESI); A/E-:APCI/ESI-MS $[M-H]^-$ (APCI/ESI means simultaneous measurement of APCI and ESI); NMR: δ (ppm) of a peak in ^{1}HNMR, and unless otherwise described, 400 MHz), Me: methyl, Et: ethyl, nPr: n-propyl, iPr: isopropyl, nBu: n-butyl, iBu: isobutyl, tBu: tert-butyl, cBu: cyclobutyl, cPr: cyclopropyl, neoPen: neopentyl, cPen: cyclopentyl, nHex: n-hexyl, cHex: cyclohexyl, cHep: cycloheptyl, cOct: cyclooctyl, Ph: phenyl, Bn: benzyl, Ac: acetyl, Boc: tert-butoxycarbonyl, Z: benzyloxycarbonyl, TBS: tert-butyldimethylsilyl, Syn: Preparation method (in which the number in the section of Syn indicates that the compound is prepared by the same method as the compound having the Preparation Example compound number or Example compound number. For example, for example, the compound of Ex2 in the section of Syn is prepared by the same method as the compound of Example 2; the compound of PEx2 in the section of Syn is prepared by the same method as the compound of Preparation Example 2; the compound of PEx1, 16 in the section of Syn is prepared by the same method as the compound of Preparation Example 1 followed by the same method as the Preparation Example 16), (cis) denotes that the relative configuration of the compound is a cis isomer, (trans) denotes that the relative configuration of the compound is a trans isomer, and (rac) denotes that the compound is a racemate, and the racemate is a mixture of an optically active body and its enantiomer (mirror image isomer) at a rate of 1:1, and means an optically inactive compound.

Furthermore, in the present specification, regarding to compounds with asymmetric carbons, when a substituent bonded to a chiral center has no notation regarding to its configuration, then it means that the configuration of the substituent has not been determined.

Furthermore, in the structural formulae in Tables as described later, when any substituent bonded to chiral centers is illustrated with a planar structure, and when there is no notation regarding the configuration of the substituent, then it means that the configuration of the substituent has not been determined.

Furthermore, for convenience, concentration mol/l is expressed as M. For example, a 1 M aqueous sodium hydroxide solution means a 1 mol/l aqueous sodium hydroxide solution.

Furthermore, the compounds of Preparation Example 29 to 100, 103, 108, 118 to 128, 132 to 134, 138, 141 to 164, 177, 202 to 238, and 241 to 277 and 202 to 279 were prepared in the same manner as the methods of Preparation Examples 1 to 28, 101 to 102, 104 to 107, 109 to 117, 129 to 131, 135 to 137, 139 to 140, and 165 to 201 as described later, and thus, they are described only in Tables as described later. For each Preparation Example Compounds, their chemical structures are shown in Tables 2 to 20 as described later and physicochemical data and preparation methods are shown in Tables 21 to 31 as described later.

Preparation Example 1

A suspension of 1 g of 5-methyl-2-nitropyridin-3-ol, 1.35 ml of (bromomethyl)cyclohexane, and 1.79 g of potassium carbonate in 10 ml of DMF was stirred at 78° C. for 12 hours. After leaving to be cooled at room temperature, to the reaction mixture were added water and hexane/ethyl acetate to carry out a layer separation operation. The organic layer was washed with water and saturated brine, and dried over anhydrous magnesium sulfate, and the solvent was evaporated under reduced pressure to obtain 1.8 g of 3-(cyclohexylmethoxy)-5-methyl-2-nitropyridine.

Preparation Example 2

To a solution of 1.8 g of 3-(cyclohexylmethoxy)-5-methyl-2-nitropyridine in 16 ml of THF was added 325 mg of 10% palladium-carbon (wet), followed by stirring for 3 hours under a hydrogen atmosphere. The reaction mixture was filtered over Celite and the solvent was then evaporated under reduced pressure to obtain 1.38 g of 3-(cyclohexylmethoxy)-5-methylpyridin-2-amine.

Preparation Example 3

To a solution of 2 g of 3-(cyclohexylmethoxy)pyridin-2-amine in 10 ml of acetic acid was added 1.90 g of N-bromosuccinimide over 30 minutes under ice-cooling, followed by stirring for 30 minutes under ice-cooling. To the reaction mixture were added water and ethyl acetate to carry out a layer separation operation. The organic layer was washed with water and saturated brine, and dried over anhydrous sodium sulfate, and the solvent was evaporated under reduced pressure. The obtained residue was purified by silica gel column chromatography to obtain 2.25 g of 5-bromo-3-(cyclohexylmethoxy)pyridin-2-amine.

Preparation Example 4

To a solution of 1.38 g of 3-(cyclohexylmethoxy)-5-methylpyridin-2-amine in 24 ml of toluene were added 1.21 ml of ethyl 2-chloro-3-oxobutanoate and 1.23 ml of triethylamine, followed by stirring at 110° C. for 3 days. After leaving to be cooled at room temperature, water and diisopropyl ether were added thereto to carry out a layer separation operation. The organic layer was dried over anhydrous sodium sulfate and the solvent was evaporated under reduced pressure. The obtained residue was purified by silica gel column chromatography to obtain 1.52 g of ethyl 8-(cyclohexylmethoxy)-2,6-dimethylimidazo[1,2-a]pyridine-3-carboxylate.

Preparation Example 5

To 2.16 g of ethyl 8-[(2-fluorobenzyl)oxy]-2-methylimidazo[1,2-a]pyridine-3-carboxylate were added 20 ml of THF, 40 ml of ethanol, and 20 ml of a 1 M aqueous sodium hydroxide solution, followed by stirring for 4 days. The solvent was evaporated under reduced pressure, and water and 1 M hydrochloric acid were added thereto. The insoluble material was collected by filtration and dried to obtain 1.99 g of 8-[(2-fluorobenzyl)oxy]-2-methylimidazo[1,2-a]pyridine-3-carboxylic acid.

Preparation Example 6

To a solution of 5.2 g of 8-(benzyloxy)-N-[(1R)-2-{[tert-butyl(dimethyl)silyl]oxy}-1-phenylethyl]-2-methylimidazo[1,2-a]pyridine-3-carboxamide in 70 ml of ethanol was added 1.0 g of 10% palladium-carbon (wet), followed by stirring for 3 hours under a hydrogen atmosphere. The reaction mixture was filtered over Celite, the solvent was then evaporated under reduced pressure, and the obtained residue was purified by silica gel column chromatography. To the obtained purified product were added hexane and diisopropyl ether, followed by stirring, and the resulting solid was collected by filtration and dried to obtain 3.5 g of N-[(1R)-2-{[tert-butyl(dimethyl)silyl]oxy}-1-phenylethyl]-8-hydroxy-2-methylimidazo[1,2-a]pyridine-3-carboxamide.

Preparation Example 7

To a solution of 2 g of methyl 3-cyclopropyl-3-oxopropanoate in 20 ml of dichloromethane was added dropwise 1.24 ml of sulfuryl chloride under ice-cooling, followed by stirring at room temperature for 5 hours. To the reaction mixture was added water under ice-cooling, and chloroform was further added thereto to carry out a layer separation operation. The organic layer was washed with saturated brine and dried over anhydrous sodium sulfate, and the solvent was evaporated under reduced pressure to obtain 2.48 g of methyl 2-chloro-3-cyclopropyl-3-oxopropanoate.

Preparation Example 8

To a suspension of 300 mg of {4-amino-1-[(benzyloxy)carbonyl]piperidin-4-yl}acetic acid in 6 ml of methanol was added 150 μl of thionyl chloride, followed by stirring for 2 days. The reaction mixture was concentrated under reduced pressure, ether was added thereto, and the resulting solid was collected by filtration and dried to obtain 350 mg of benzyl 4-amino-4-(2-methoxy-2-oxoethyl)piperidine-1-carboxylate hydrochloride.

Preparation Example 9

To a solution of 1.07 g of tert-butyl(diethoxyphosphoryl)acetate in 50 ml of THF was added 3.8 ml of a 1.12 M methylmagnesium bromide/THF solution, followed by stirring for 30 minutes. To the obtained reaction mixture was added a solution of 500 of n-pentanal in 5 ml of THF, followed by heating to reflux for 3 hours. To the reaction mixture were added a saturated aqueous ammonium chloride solution and ether to carry out a layer separation operation. The organic layer was washed with saturated brine and dried over anhydrous magnesium sulfate, and the solvent was evaporated under reduced pressure to obtain 726 mg of tert-butyl (2E)-hepta-2-noate.

Preparation Example 10

To a solution of 1.3 ml of (1R)—N-benzyl-1-phenylethanamine in 15 ml of THF was added 3.7 ml of a 1.65 M n-butyllithium/hexane solution at −78° C., followed by stirring at the same temperature for 1 hour. Then, a solution of 710 mg of tert-butyl (2E)-hepta-2-noate in 5 ml of THF was slowly added dropwise at the same temperature, followed by stirring at the same temperature for 3 hours. To the reaction mixture was added a saturated aqueous ammonium chloride solution, followed by warming to room temperature, and ethyl acetate was added thereto to carry out a layer separation operation. The organic layer was washed with saturated brine and dried over anhydrous magnesium sulfate, and the solvent was evaporated under reduced pressure. The obtained residue was purified by silica gel column chromatography to obtain 1.27 g of tert-butyl (3R)-3-{benzyl[(1R)-1-phenylethyl]amino}heptanoate. Further, the structure of the product was determined in accordance to a reference (Tetrahedron Asymmetry, 17 (2006) 1793-1811, and the like) by S. G. Davis, et al.

Preparation Example 11

To a solution of 1.15 g of tert-butyl (3R)-3-{benzyl[(1R)-1-phenylethyl]amino}heptanoate in 30 ml of methanol was added 450 mg of 10% palladium-carbon, followed by stirring overnight under a hydrogen atmosphere at 4 atm. The reaction mixture was filtered over Celite and the solvent was then evaporated under reduced pressure. The obtained residue was purified by silica gel column chromatography to obtain 460 mg of tert-butyl (3R)-3-aminoheptanoate.

Preparation Example 12

To a suspension of 510 mg of 8-(cyclohexylmethoxy)-2-methylimidazo[1,2-a]pyridine-3-carboxylic acid in dichloromethane were added 0.30 ml of oxalyl dichloride and one drop of DMF under ice-cooling, followed by stirring at room temperature for 30 minutes, and the solvent was evaporated under reduced pressure to obtain 603 mg of 8-(cyclohexylmethoxy)-2-methylimidazo[1,2-a]pyridine-3-carboxylic acid chloride hydrochloride.

Preparation Example 13

To a solution of 2 g of methyl 5-hydroxy-6-nitronicotinate, 1.62 ml of (2-fluorophenyl)methanol, and 3.99 ml of tributylphosphine in 40 ml of THF was added 2.54 ml of diethyl azodicarboxylate under ice-cooling, followed by stirring for 1 hour under ice-cooling and at room temperature for 2 hours. To the reaction mixture were added water and ethyl acetate to carry out a layer separation operation. The organic layer was washed with saturated brine and dried over anhydrous magnesium sulfate, and the solvent was evaporated under reduced pressure. The obtained residue was purified by silica gel column chromatography to obtain 2.58 g of methyl 5-[(2-fluorobenzyl)oxy]-6-nitronicotinate.

Preparation Example 14

To a solution of 2.5 g of methyl 5-[(2-fluorobenzyl)oxy]-6-nitronicotinate in 25 ml of THF were added 50 ml of ethanol, 25 ml of water, 218 mg of ammonium chloride, and 1.37 g of iron, followed by heating to reflux for 2 hours. After leaving to be cooled at room temperature, the reaction mixture was filtered over Celite, and to the filtrate were added a saturated aqueous sodium hydrogen carbonate solution and chloroform to carry out a layer separation operation. The organic layer was dried over anhydrous sodium sulfate and the solvent was evaporated under reduced pressure to obtain 2.25 g of methyl 6-amino-5-[(2-fluorobenzyl)oxy]nicotinate.

Preparation Example 15

To a suspension of 2.15 g of methyl 6-amino-5-[(2-fluorobenzyl)oxy]nicotinate in 43 ml of ethanol was added 1.09 ml of bromoacetone, followed by stirring at 80° C. for 4 hours. To the reaction mixture was added 1.09 ml of bromoacetone, followed by stirring at 80° C. for 4 hours. To the reaction mixture was added a saturated aqueous sodium hydrogen carbonate solution, and the solvent was evaporated under reduced pressure, followed by extracting with ethyl acetate and washing with saturated brine. After drying over anhydrous magnesium sulfate and then filtering, the solvent was evaporated under reduced pressure. The obtained residue was purified by silica gel column chromatography to obtain 1.39 g of methyl 8-[(2-fluorobenzyl)oxy]-2-methylimidazo[1,2-a]pyridine-6-carboxylate.

Preparation Example 16

To 350 mg of 8-[(2-fluorobenzyl)oxy]-2-methylimidazo[1,2-a]pyridine-6-carboxylic acid were added 18 ml of ethanol and 200 μl of sulfuric acid, followed by heating to reflux overnight. Under reduced pressure, the solvent was removed by filtration to around one third of the amount thereof, and a saturated aqueous sodium hydrogen carbonate solution and chloroform were then added thereto to carry out a layer separation operation. The organic layer was dried over anhydrous sodium sulfate and the solvent was evaporated under reduced pressure. The obtained residue was purified by silica gel column chromatography to obtain 330 mg of ethyl 8-[(2-fluorobenzyl)oxy]-2-methylimidazo[1,2-a]pyridine-6-carboxylate.

Preparation Example 17

A mixture of 1 g of N-methyl-2-nitrobenzenesulfonamide, 2.3 g of tert-butyl [(1R)-2-hydroxy-1-phenylethyl]carbamate, 2.5 g of triphenylphosphine, 4.2 ml of diethyl azodicarboxylate, and 40 ml of toluene was stirred at 80° C. for 2 hours, and the solvent was evaporated under reduced pressure. To a solution of the obtained residue in chloroform was added silica gel, followed by filtration, and the filtrate was concentrated under reduced pressure. To a solution of the obtained residue in 3 ml of dichloromethane was added 3 ml of trifluoroacetic acid, followed by stirring for 1 hour. The solvent was evaporated under reduced pressure, and an aqueous sodium carbonate solution and chloroform were then added thereto to carry out a layer separation operation. The organic layer was dried over anhydrous magnesium sulfate and the solvent was evaporated under reduced pressure. The obtained residue was purified by silica gel column chromatography to obtain 890 mg of N-[(2R)-2-amino-2-phenylethyl]-N-methyl-2-nitrobenzenesulfonamide.

Preparation Example 18

To a solution of 200 mg of 8-(cyclohexylmethoxy)-N-(2,2-dimethoxyethyl)-2-methylimidazolo[1,2-a]pyridine-3-carboxamide in 2 mL of dioxane was added 6 M hydrochloric acid, followed by stirring for 7 hours. To the reaction mixture were added saturated brine and ethyl acetate to carry out a layer separation operation. To the obtained aqueous layer was added a 1 M aqueous sodium hydroxide solution, and the resulting solid was collected by filtration and dried to obtain 165 mg of 8-(cyclohexylmethoxy)-2-methyl-N-(2-oxoethyl)imidazolo[1,2-a]pyridine-3-carboxamide.

Preparation Example 19

To a solution of 160 mg of ethyl 1-{(2R)-2-[(tert-butoxycarbonyl)amino]-2-phenylethyl}piperidine-4-carboxylate in 1.5 mL of dichloromethane was added 0.7 mL of trifluoroacetic acid, followed by stirring for 1 hour. The solvent was evaporated under reduced pressure, and a saturated aqueous sodium carbonate solution and a chloroform-methanol mixed solution were added thereto in this order to carry out a layer separation operation. After drying over anhydrous magnesium sulfate, the solvent was evaporated under reduced pressure to obtain 120 mg of ethyl 1-[(2R)-2-amino-2-phenylethyl]piperidine-4-carboxylate.

Preparation Example 20

To a solution of 1 g of (2R)-2-[(tert-butoxycarbonyl)amino]-2-phenylethyl methanesulfonate in 5 mL of THF were added 0.4 mL of ethyl piperidine-4-carboxylate and 1 mL of diisopropylethylamine, followed by stirring at 70° C. for 14 hours, and the solvent was evaporated under reduced pressure. The obtained residue was purified by silica gel column chromatography to obtain 160 mg of ethyl 1-{(2R)-2-[(tert-butoxycarbonyl)amino]-2-phenylethyl}piperidine-4-carboxylate.

Preparation Example 21

To 223 mg of tert-butyl (2E)-3-(4-cyanophenyl)acrylate were added 12 mL of methanol, 5 ml of THF, 1 ml of an acetic acid solution, and 90 mg of 10% palladium-carbon in this order, followed by stirring for 3 hours under hydrogen at 3 atm. The catalyst was removed by filtration and the filtrate was concentrated under reduced pressure. To the residue were added a saturated aqueous sodium hydrogen carbonate solution and ethyl acetate to carry out a layer separation operation. The organic layer was dried over anhydrous sodium sulfate and the solvent was evaporated under reduced pressure to obtain 177 mg of tert-butyl 3-[4-(aminomethyl)phenyl]propanoate.

Preparation Example 22

To a solution of 280 mg of ethyl 2-(4-cyanophenyl)-2-methylpropanoate in 10 ml of ethanol were added 2 mL of 1 M hydrochloric acid and 120 mg of 10% palladium-carbon in this order, followed by stirring for 3 hours under a hydrogen atmosphere at 3 atm. The catalyst was removed by filtration, and the filtrate was concentrated under reduced pressure and dried to obtain 345 mg of, ethyl 2-[4-(aminomethyl)phenyl]-2-methylpropanoate hydrochloride.

Preparation Example 23

A mixture of 1 g of tert-butyl (2-bromobenzyl)carbamate, 1.12 g of ethyl (2E)-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)acrylate, 16 mg of palladium acetate, 72 mg of dicyclohexyl(2',6'-dimethoxybiophenyl-2-yl)phosphine, 1.5 g of potassium phosphate, and 20 mL of toluene was stirred at 100° C. for 5 days. To the reaction mixture was added ether, followed by filtration through silica gel. The filtrate was concentrated under reduced pressure and the obtained residue was purified by silica gel column chromatography to obtain 412 mg of ethyl (2E)-3-(2-{[(tert-butoxycarbonyl)amino]methyl}phenyl)acrylate.

Preparation Example 24

To a suspension of 320 mg of 60% sodium hydride in 4 mL of DMF were added 500 mg of ethyl(4-cyanophenyl)acetate and a solution of 0.41 mL of methyl iodide in 2 mL of DMF under ice-cooling, followed by stirring at room temperature for 1 day. To the reaction mixture were added water and ethyl acetate to carry out a layer separation operation. The organic layer was washed with water and saturated brine in this order, and dried over anhydrous sodium sulfate, and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography to obtain 280 mg of ethyl 2-(4-cyanophenyl)-2-methylpropanoate.

Preparation Example 25

To a solution of 1 g of (3S)-3-amino-2-hydroxyhexanoic acid hydrochloride in 10 mL of methanol was added 10 mL of a 4 M hydrogen chloride/dioxane solution, followed by stirring overnight, and the solvent was evaporated under reduced pressure. A saturated aqueous sodium hydrogen carbonate solution and chloroform were added thereto to carry out a layer separation operation. The organic layer was washed with saturated brine and dried over anhydrous sodium sulfate and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography to obtain 425 mg of methyl (2R,3S)-3-amino-2-hydroxyhexanoate and 130 mg of methyl (2S,3S)-3-amino-2-hydroxyhexanoate.

Preparation Example 26

To a solution of 500 mg of tert-butyl (3S)-piperidin-3-yl carbamate and 900 mg of [3-(methoxycarbonyl)phenyl]boric acid in 10 mL of dichloromethane were added Molecular Sieves 4A, 460 mg of copper (II) acetate, and 0.70 mL of triethylamine in this order, followed by stirring overnight. The reaction mixture was filtered over Celite, and then to the filtrate were added a saturated aqueous sodium hydrogen carbonate solution and ethyl acetate to carry out a layer separation operation. The organic layer was washed with saturated brine and then dried over anhydrous magnesium sulfate, and the solvent was evaporated under reduced pressure. The obtained residue was purified by silica gel column chromatography to obtain 380 mg of methyl 3-{(3S)-3-[(tert-butoxycarbonyl)amino]piperidin-1-yl}benzoate.

Preparation Example 27

To a solution of 300 mg of tert-butyl (3S)-piperidin-3-yl carbamate and 6 mL of N-methyl-2-pyrrolidone were added 310 mg of methyl 6-chloropyridine-2-carboxylate and 0.55 mL of diisopropylethylamine, followed by stirring at 130° C. overnight. After leaving to be cooled, to the reaction mixture were added water and ethyl acetate to carry out a layer separation operation. The organic layer was washed with saturated brine and dried over anhydrous magnesium sulfate, and the solvent was evaporated under reduced pressure. The obtained residue was purified by silica gel column chromatography to obtain 215 mg of methyl 6-{(3S)-3-[(tert-butoxycarbonyl)amino]piperidin-1-yl}pyridine-2-carboxylate.

Preparation Example 28

To 2.02 g of tert-butyl (3S)-piperidin-3-yl carbamate were added 4.86 g of sulfamide and 30 mL of dioxane, followed by stirring at 95° C. overnight. After leaving to be cooled, the solvent was evaporated under reduced pressure, and water and chloroform were added thereto to carry out a layer separation operation. The organic layer was washed with an aqueous citric acid solution and dried over anhydrous magnesium sulfate, and the solvent was evaporated under reduced pressure. To the obtained residue was added 30 mL of a 4 M hydrogen chloride-ethyl acetate solution, followed by stirring for 40 minutes. The resulting solid was collected by filtration and dried to obtain 1.51 g of (3S)-3-aminopiperidine-1-sulfonamide hydrochloride.

Preparation Example 101

To 2.36 g of 2a,3,4,8b-tetrahydronaphtho[1,2-b]azet-2(1H)-one was added 50 ml of a 10% hydrogen chloride/methanol solution, followed by stirring at 90° C. for 6 hours. After leaving to be cooled, the solvent was evaporated under reduced pressure. To the obtained residue were added methanol and diethyl ether, and the insoluble material was collected by filtration and dried to obtain 3.08 g of methyl rac-(1S,2S)-1-amino-1,2,3,4-tetrahydronaphthalene-2-carboxylate hydrochloride.

Preparation Example 102

To a suspension of 750 mg of rac-(1R,2R)-1-[(tert-butoxycarbonyl)amino]indane-2-carboxylic acid in 15 ml of methanol was added 0.40 ml of thionyl chloride, followed by stirring overnight. The solvent was evaporated to about a half amount thereof under reduced pressure, to the obtained residue was added diethyl ether, and the insoluble material was collected by filtration and dried to obtain 512 mg of methyl rac-(1R,2R)-1-aminoindane-2-carboxylate hydrochloride.

Preparation Example 104

A mixture of 2.64 g of (2-bromo-5-methylphenyl)methanol, 246 mg of bis(dibenzylideneacetone)palladium, 2.95 ml of tert-butylacrylate, 442 mg of tris(2-methylphenyl)phosphine, 2.5 ml of triethylamine, and 24 ml of DMF was stirred at 100° C. for 24 hours. After leaving to be cooled at room temperature, water and ethyl acetate were added thereto to carry out a layer separation operation. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate, and the solvent was evaporated under reduced pressure. The obtained residue was purified by silica gel column chromatography to obtain 2.32 g of tert-butyl (2E)-3-[2-(hydroxymethyl)-4-methylphenyl]acrylate.

Preparation Example 105

To a solution of 2.32 g of tert-butyl (2E)-3-[2-(hydroxymethyl)-4-methylphenyl]acrylate in 46 ml of THF were added 4.64 g of carbon tetrabromide and 3.67 g of triphenylphosphine under ice-cooling, followed by stirring at the same temperature for 2.5 hours. To the reaction mixture were added water and ethyl acetate to carry out a layer separation operation. The organic layer was washed with water and saturated brine in this order, and dried over anhydrous magnesium sulfate, and the solvent was evaporated under reduced pressure. The obtained residue was purified by silica gel column chromatography to obtain 2.73 g of tert-butyl (2E)-3-[2-(bromomethyl)-4-methylphenyl]acrylate.

Preparation Example 106

To a solution of 1.5 ml of (1R)—N-benzyl-1-phenylethanamine in 40 ml of THF was added 4.35 ml of n-butyllithium (1.62 M hexane solution) at −78° C., followed by stirring for 30 minutes. At the same temperature, a solution of 1.00 g of tert-butyl (2E)-3-[2-(bromomethyl)-4-methylphenyl]acrylate in 5 ml of THF was added thereto, followed by stirring for 1.5 hours. To the reaction mixture was added water, followed by warming to room temperature. The solvent was evaporated under reduced pressure and ethyl acetate was then added thereto to carry out a layer separation operation. The organic layer was washed with a 1 M aqueous citric acid solution, water, and saturated brine in this order, and dried over anhydrous magnesium sulfate, and the solvent was evaporated under reduced pressure. The obtained residue was purified by silica gel column chromatography to obtain 1.17 g of tert-butyl (1S,2R)-1-{benzyl[(1R)-1-phenylethyl]amino}-5-methylindane-2-carboxylate. Further, the present Preparation Example is in accordance with the method described in a reference (Synlett, 1999, No. 12, 1919-1920 by D. A. Price).

Preparation Example 107

To 1.10 g of tert-butyl (1S,2R)-1-{benzyl[(1R)-1-phenylethyl]amino}-5-methylindane-2-carboxylate was added 30 ml of a 10% hydrogen chloride/methanol solution, followed by stirring at 60° C. for 5 hours. After leaving to be cooled, the solvent was evaporated under reduced pressure, and a saturated aqueous sodium hydrogen carbonate solution and ethyl acetate were added thereto to carry out a layer separation operation. The organic layer was washed with saturated brine and dried over anhydrous magnesium sulfate, and the solvent was evaporated under reduced pressure. The obtained residue was purified by silica gel column chromatography to obtain 828 mg of methyl S,2R)-1-{benzyl[(1R)-1-phenylethyl]amino}-5-methylindane-2-carboxylate.

Preparation Example 109

To a solution of 1.67 g of methyl (1S,2R)-1-{benzyl[(1R)-1-phenylethyl]amino}-6-methylindane-2-carboxylate in 27 ml of acetic acid was added 500 mg of 10% palladium-carbon (wet), followed by stirring for 18 hours under a hydrogen atmosphere at 4 atm. The reaction mixture was filtered over Celite and the solvent was then evaporated under reduced pressure. To the obtained residue were added a saturated aqueous sodium hydrogen carbonate solution, chloroform, and methanol to carry out a layer separation operation. The organic layer was washed with saturated brine and dried over anhydrous magnesium sulfate, the solvent was evaporated under reduced pressure, and the obtained residue was purified by silica gel column chromatography. To a solution of the obtained purified product in methanol was added 3 ml of a 10% hydrogen chloride/methanol solution. The solvent was evaporated under reduced pressure to obtain 803 mg of methyl (1S,2R)-1-amino-6-methylindane-2-carboxylate hydrochloride.

Preparation Example 110

To a solution of 789 mg of tert-butyl (2E)-3-[2-(hydroxymethyl)-3-methylphenyl]acrylate in 16 ml of methanol was added 82 mg of nickel chloride (II). Then, 240 mg of sodium borohydride was added thereto under ice-cooling, followed by stirring for 4 hours under ice-cooling. To the reaction mixture were added water and ethyl acetate to carry out a layer separation operation. The organic layer was washed with saturated brine and dried over anhydrous magnesium sulfate, and the solvent was evaporated under reduced pressure to obtain 790 mg of tert-butyl 3-[2-(hydroxymethyl)-3-methylphenyl]propanoate.

Preparation Example 111

To a solution of 770 mg of tert-butyl 3-[2-(hydroxymethyl)-3-methylphenyl]propanoate in 16 ml of dimethylsulfoxide were added 4 ml of triethylamine and 1.22 g of a sulfur trioxide pyridine complex, followed by stirring at room temperature for 5 hours. To the reaction mixture were added diluted hydrochloric acid and ethyl acetate to carry out a layer separation operation. The organic layer was sequentially washed with water, saturated aqueous sodium hydrogen carbonate solution, water, and saturated brine, dried over anhydrous magnesium sulfate, and the solvent was evaporated under reduced pressure. The obtained residue was purified by silica gel column chromatography to obtain 707 mg of tert-butyl 3-(2-formyl-3-methylphenyl) propanoate.

Preparation Example 112

To a solution of 305 mg of tert-butyl 3-(2-formyl-3-methylphenyl)propanoate in 3 ml of THF 3 ml were added 298 mg of (S)-2-methyl-2-propanesulfinamide and 0.62 ml of tetraethyl orthotitanate, followed by stirring at room temperature for 16 hours. The reaction mixture was poured into ice water and the insoluble material was filtered through Celite. To the filtrate was added chloroform to carry out a layer separation operation. The organic layer was washed with water and subsequentially with saturated brine, dried over anhydrous magnesium sulfate, and the solvent was evaporated under reduced pressure. The obtained residue was purified by silica gel column chromatography to obtain 336 mg of tert-butyl 3-{2-[(E)-{[(S)-tert-butylsulfinyl] imino}methyl]-3-methylphenyl}propanoate.

Preparation Example 113

To a solution of 1.122 g of tert-butyl 3-{2-[(E)-{[(S)-tert-butylsulfinyl]imino}methyl]-3-fluorophenyl}propanoate (compound of Preparation Example 129) in 26.7 ml of THF was added 9.5 ml of lithium bis(trimethylsilyl)amide (1 M THF solution) at −78° C., followed by stirring at the same temperature for 8.5 hours. To the reaction mixture were added a saturated aqueous ammonium chloride solution and ethyl acetate to carry out a layer separation operation. The organic layer was washed with saturated brine and dried over anhydrous magnesium sulfate, and the solvent was evaporated under reduced pressure. The obtained residue was purified by silica gel column chromatography to obtain 390 mg of tert-butyl (1S,2R)-1-{[(S)-tert-butylsulfinyl] amino}-7-fluoroindane-2-carboxylate (Preparation Example 113a), and 130 mg of each of tert-butyl (1R,2R)-1-{[(S)-tert-butylsulfinyl]amino}-7-fluoroindane-2-carboxylate and tert-butyl (1S,2S)-1-{[(S)-tert-butylsulfinyl]amino}-7-fluoroindane-2-carboxylate (Preparation Example 113b and Preparation Example 113c).

Preparation Example 114

To a solution of 140 mg of tert-butyl (1S,2R)-1-{[(S)-tert-butylsulfinyl]amino}-7-methylindane-2-carboxylate in 9.1 ml of ethyl acetate was added 0.88 ml of a 4 M hydrogen chloride/ethyl acetate solution, followed by stirring at room temperature for 2 hours. The solvent was evaporated under reduced pressure, and to the obtained residue were added a saturated aqueous sodium hydrogen carbonate solution and ethyl acetate to carry out a layer separation operation. The organic layer was washed with water and saturated brine, and dried over anhydrous magnesium sulfate, and the solvent was evaporated under reduced pressure to obtain 88 mg of tert-butyl (1S,2R)-1-amino-7-methylindane-2-carboxylate.

Preparation Example 115

To 12 mg of tert-butyl (1S,2R)-1-{[(S)-tert-butylsulfinyl] amino}-7-fluoroindane-2-carboxylate (compound of Preparation Example 113a) was added 0.4 ml of a 10% hydrogen chloride/methanol solution, followed by stirring for 1 hour under ice-cooling. To the reaction mixture was added 1 ml of a 10% hydrogen chloride/methanol solution, followed by stirring at 50° C. for 6 hours. After leaving to be cooled, the solvent was evaporated under reduced pressure, and then to the obtained residue were added a saturated aqueous sodium hydrogen carbonate solution and ethyl acetate to carry out a layer separation operation. The organic layer was washed with saturated brine and dried over anhydrous magnesium sulfate, and the solvent was evaporated under reduced pressure to obtain 6 mg of methyl (1S,2R)-1-amino-7-fluoroindane-2-carboxylate.

Preparation Example 116

A suspension of 1 g of 2-bromothiophene-3-carbaldehyde, 3.8 ml of tert-butyl acrylate, 120 mg of palladium acetate, 420 mg of tetra-n-butylammonium bromide, and 610 mg of potassium carbonate in 10 ml of DMF was stirred at 100° C. overnight. After leaving to be cooled, the insoluble material was filtered through Celite, and to the filtrate were added water and ethyl acetate to carry out a layer separation operation. The organic layer was washed with saturated brine and dried over anhydrous magnesium sulfate, and the solvent was evaporated under reduced pressure. The obtained residue was purified by silica gel column chromatography to obtain 660 mg of tert-butyl (2E)-3-(3-formyl-2-thienyl)acrylate.

Preparation Example 117

To a solution of 650 mg of tert-butyl (2E)-3-(3-formyl-2-thienyl)acrylate in 15 ml of methanol was added 150 mg of 10% palladium-carbon, followed by stirring for 5 hours under a hydrogen atmosphere. After filtration through Celite, the solvent was evaporated under reduced pressure. The obtained residue was purified by silica gel column chromatography to obtain 530 mg of tert-butyl 3-(3-formyl-2-thienyl)propanoate.

Preparation Example 129

tert-Butyl 3-{2-[(E)-{[(S)-tert-butylsulfinyl] imino}methyl]-3-fluorophenyl}propanoate was prepared using (S)-2-methyl-2-propanesulfinamide by the same method as in Preparation Example 112 as described above.

Preparation Example 130

tert-Butyl 3-(2-{(E)-[(tert-butylsulfinyl)imino]methyl}-3-fluorophenyl)propanoate as a racemate was prepared using 2-methyl-2-propanesulfinamide as a racemate by the same method as in Preparation Example 112 as described above.

Preparation Example 131

tert-Butyl 3-{2-[(E)-{[(R)-tert-butylsulfinyl] imino}methyl]-3-fluorophenyl}propanoate was prepared using (R)-2-methyl-2-propanesulfinamide by the same method as in Preparation Example 112 as described above.

Preparation Example 135

tert-Butyl rac-(1R,2R)-1-[(tert-butylsulfinyl)amino]-7-fluoroindane-2-carboxylate was prepared using tert-butyl 3-(2-{(E)-[(tert-butylsulfinyl)imino]methyl}-3-fluorophenyl)propanoate (compound of Preparation Example 130) as a racemate by the same method as in Preparation Example 113 as described above.

Preparation Example 136

tert-Butyl (1R,2S)-1-[(R)-tert-butylsulfinyl]amino-7-fluoroindane-2-carboxylate was prepared using tert-butyl 3-{2-[(E)-{[(R)-tert-butylsulfinyl]imino}methyl]-3-fluorophenyl}propanoate (compound of Preparation Example 131) by the same method as in Preparation Example 113 as described above. Further, the compound of Preparation Example 136 and the compound of Preparation Example 113a are enantiomers (mirror image isomers) with respect to each other.

Preparation Example 137

To a solution of 120 mg of tert-butyl (5R,6S)-4-{[(S)-tert-butylsulfinyl]amino}-5,6-dihydro-4H-cyclopenta[b]thiophene-5-carboxylate (compound of Preparation Example 143) in 7 ml of ethyl acetate was added 0.7 ml of a 4 M hydrogen chloride/ethyl acetate solution, followed by stirring for 2 hours. The solvent was evaporated under reduced pressure, and then to the obtained residue was added diisopropyl ether. The insoluble material was collected by filtration and dried to obtain 80 mg of tert-butyl (5R,6S)-6-amino-5,6-dihydro-4H-cyclopenta[b]thiophene-5-carboxylate hydrochloride.

Preparation Example 139

Preparation was carried out using the compound of Preparation Example 135 by the same method as in Preparation Example 115 as described above.

Preparation Example 140

Preparation was carried out using the compound of Preparation Example 136 by the same method as in Preparation Example 115 as described above. Further, the compound of Preparation Example 140 and the compound of Preparation Example 115 are enantiomers (mirror image isomers) with respect to each other.

Preparation Example 165

To 820 mg of tert-butyl[(1S)-1-(3-bromophenyl)ethyl]carbamate were added 113 mg of 1,3-bis(diphenylphosphino)propane, 62 mg of palladium acetate, 0.84 ml of triethylamine, 8 ml of DMF, and 12 ml of methanol, followed by stirring at room temperature for 1 hour. While stirring at room temperature, carbon monooxide was intaken for 10 minutes, followed by stirring at 80° C. overnight under a carbon monooxide atmosphere. 113 mg of 1,3-bis(diphenylphosphino)propane and 62 mg of palladium acetate were added thereto, followed by stirring at 80° C. overnight. To the reaction mixture were added water and ethyl acetate to carry out a layer separation operation. The organic layer was washed with saturated brine and dried over anhydrous magnesium sulfate, and the solvent was evaporated under reduced pressure. The obtained residue was purified by silica gel column chromatography to obtain 577 mg of methyl 3-{(1S)-1-[(tert-butoxycarbonyl)amino]ethyl}benzoate.

Preparation Example 166

To a solution of 1 g of tert-butyl[(1R,2R)-2-hydroxy-2,3-dihydro-1H-inden-1-yl]carbamate in 10 ml of THF was added 16.9 ml of a 0.5 M potassium hexamethyldisilazane/toluene solution at −78° C., followed by stirring for 30 minutes. 0.92 ml of chlorodimethyl ether was added thereto at −78° C., followed by warming to room temperature for 3 hours. 4 ml of a 0.5 M potassium hexamethyldisilazane/toluene solution and 0.31 ml of chlorodimethyl ether were added thereto at −78° C., followed by stirring at room temperature for 2 hours. To the reaction mixture were added a saturated aqueous ammonium chloride solution and ethyl acetate to carry out a layer separation operation. The organic layer was washed with saturated brine and dried over anhydrous magnesium sulfate, and the solvent was evaporated under reduced pressure. The obtained residue was purified by silica gel column chromatography to obtain 311 mg of tert-butyl [(1R,2R)-2-(methoxymethoxy)-2,3-dihydro-1H-inden-1-yl](methoxymethyl)carbamate.

Preparation Example 167

A solution of 2.75 g of tert-butyl[(1R,2R)-2-(methoxymethoxy)-2,3-dihydro-1H-inden-1-yl](methoxymethyl)carbamate in 55 ml of carbon tetrachloride was heated at an outer temperature of 100° C., and a mixture of 1.53 g of N-bromosuccinimide and 95 mg of 2,2'-azodiisobutyronitrile was added portionwise thereto over 30 minutes at an interval of 5 minutes, followed by stirring at an outer temperature of 100° C. for 1 hour. The insoluble material was filtered, and an aqueous sodium thiosulfate solution and chloroform were added thereto to carry out a layer separation operation. After drying over anhydrous sodium sulfate, the solvent was evaporated under reduced pressure. The obtained residue was purified by silica gel column chromatography to obtain 984 mg of tert-butyl[(1R,2S)-3-bromo-2-(methoxymethoxy)-2,3-dihydro-1H-inden-1-yl](methoxymethyl)carbamate.

Preparation Example 168

To 983 mg of tert-butyl[(1R,2S)-3-bromo-2-(methoxymethoxy)-2,3-dihydro-1H-inden-1-yl](methoxymethyl)carbamate were added 1.39 g of potassium acetate and 15 ml of N-methyl-2-pyrrolidone, followed by stirring at 70° C. for 15 hours. To the reaction mixture were added water and ethyl acetate to carry out a layer separation operation. The organic layer was washed with water and saturated brine, and dried over anhydrous sodium sulfate, and the solvent was evaporated under reduced pressure. The obtained residue was purified by silica gel column chromatography to obtain 436 mg (Preparation Example 168a) and 106 mg (Preparation Example 168b), respectively, of (2S,3R)-3-[(tert-butoxycarbonyl)(methoxymethyl)amino]-2-(methoxymethoxy)-2,3-dihydro-1H-inden-1-yl acetate, as two kinds of single isomers, each having an undetermined configuration at the 1-position of an indane ring.

Preparation Example 169

To 235 mg of tert-butyl (3aR,8aR)-8-acetoxy-2-oxo-8,8a-dihydro-2H-indeno[1,2-d][1,3]oxazole-3(3aH)-carboxylate were added 2.4 ml of THF, 0.24 ml of water, and 229 mg of sodium hydroxide, followed by stirring for 4 hours. To the reaction mixture were added water and chloroform to carry out a layer separation operation. The organic layer was washed with saturated brine and dried over anhydrous magnesium sulfate, and the solvent was evaporated under reduced pressure. The obtained residue was purified by silica gel column chromatography to obtain 66 mg (Preparation Example 169a) and 28 mg (Preparation Example 169b), respectively, of tert-butyl[(1R,2R)-2,3-dihydroxy-2,3-dihydro-1H-inden-1-yl]carbamate, as two kinds of single isomers, each having an undetermined configuration at the 3-position of an indane ring.

Preparation Example 170

To a solution of 700 mg of tert-butyl[(1R,2R)-3-{[tert-butyl(dimethyl)silyl]oxy}-2-hydroxy-1-phenylpropyl]carbamate in 35 ml of THF was added 1.2 g of triphenylphosphine, 766 mg of 4-nitrobenzoic acid, and 2.4 ml of a 1.9 M diisopropyl azodicarboxylate/toluene solution under ice-cooling, followed by stirring at room temperature for 5 hours. To the reaction mixture were added water and ethyl acetate to carry out a layer separation operation. The organic layer was washed with saturated brine and dried over anhydrous magnesium sulfate, and the solvent was evaporated under reduced pressure. The obtained residue was purified by silica gel column chromatography to obtain 638 mg of (6S,7R)-2,2,3,3,11,11-hexamethyl-9-oxo-7-phenyl-4,10-dioxa-8-aza-3-siladodecan-6-yl 4-nitrobenzoate.

Preparation Example 171

To a solution of 106 mg of the compound of Preparation Example 168b in 6 ml of methanol was added 117 mg of potassium carbonate, followed by stirring for 2 hours. To the reaction mixture were added water and ethyl acetate to carry out a layer separation operation, the organic layer was dried over anhydrous sodium sulfate, and the solvent was evaporated under reduced pressure. The obtained residue was purified by silica gel column chromatography to obtain 82 mg of tert-butyl[(1R,2S)-3-hydroxy-1-(methoxymethoxy)-2,3-dihydro-1H-inden-1-yl](methoxymethyl)carbamate as a single isomer having an undetermined configuration at the 3-position of an indane ring.

Preparation Example 172

To a solution of 190 mg of the compound of Preparation Example 171 in 3 ml of methanol was added 3 ml of 4 M hydrogen chloride/dioxane solution, followed by stirring for 20 hours. The solvent was evaporated under reduced pressure to obtain 110 mg of (2S,3R)-3-aminoindane-1,2-diol hydrochloride as a compound having an undetermined configuration at the 1-position of an indane ring. This was used for the next step without purification.

Preparation Example 173

To a solution of 1 g of methyl 3-oxoindane-1-carboxylate in 10 ml of toluene were added 0.78 ml of (1S)-1-(4-methoxyphenyl)ethanamine and 100 mg of p-toluenesulfonic acid monohydrate, followed by heating to reflux for 5 hours using a Dean-Stark type reflux device. Then, 634 mg of magnesium sulfate was added thereto, followed by heating to reflux for 5 hours using a Dean-Stark type reflux device. Further, 634 mg of magnesium sulfate was added thereto, followed by heating to reflux for 5 hours using a Dean-Stark type reflux device. The insoluble material was removed by filtration and the solvent was then evaporated under reduced pressure to obtain an intermediate product. To a solution of the obtained intermediate product in 17 ml of ethanol was added 209 mg of sodium borohydride under ice-cooling, followed by stirring for 1 hour under ice-cooling. The solvent was evaporated under reduced pressure, and to the obtained residue were added water, a saturated aqueous sodium hydrogen carbonate solution, and ethyl acetate to carry out a layer separation operation. The organic layer was washed with water and saturated brine, and dried over anhydrous magnesium sulfate, and the solvent was evaporated under reduced pressure. The obtained residue was purified by silica gel column chromatography to obtain 1.195 g of methyl (3S)-3-{[(1S)-1-(4-methoxyphenyl)ethyl]amino}indane-1-carboxylate.

Preparation Example 174

To 713 mg of methyl 1-oxoindane-5-carboxylate were added 612 mg of (1S)-1-(4-methoxyphenyl)ethanamine, 0.23 ml of acetic acid, 600 mg of Molecular Sieves 4A, and 12 ml of toluene, followed by heating to reflux using a Dean-Stark type reflux device for 4 hours under reduced pressure (213 mbar). Then, 0.23 ml of acetic acid and 300 mg of Molecular Sieves 4A were added thereto, followed by heating to reflux using a Dean-Stark type reflux device for 4 hours under reduced pressure (213 mbar). The insoluble material was removed by filtration and the solvent was then evaporated under reduced pressure to obtain an intermediate product. To a solution of the obtained intermediate product in 13 ml of ethanol was added 161 mg of sodium borohydride under ice-cooling, followed by stirring for 1 hour under ice-cooling. The solvent was evaporated under reduced pressure, and to the obtained residue were added water, a saturated aqueous sodium hydrogen carbonate solution, and ethyl acetate to carry out a layer separation operation. The organic layer was washed with water and saturated brine in this order, and dried over anhydrous magnesium sulfate, and the solvent was evaporated under reduced pressure. The obtained residue was purified by silica gel column chromatography to obtain 452 mg of methyl (1S)-1-{[(1S)-1-(4-methoxyphenyl)ethyl]amino}indane-5-carboxylate.

Preparation Example 175

To a solution of 850 mg of tert-butyl[2-(3-bromophenyl)propan-2-yl]carbamate in 8.5 ml of THF was added 4.1 ml of a 1.65 M n-butyllithium/hexane solution at −78° C., followed by stirring at the same temperature for 30 minutes. Then, 0.85 ml of methyl chloroformate was added dropwise thereto at −78° C., followed by stirring at the same temperature for 1 hour. To the reaction mixture were added a saturated aqueous ammonium chloride solution and ethyl acetate to carry out a layer separation operation. The organic layer was washed with saturated brine and dried over anhydrous magnesium sulfate, and the solvent was evaporated under reduced pressure. The obtained residue was purified by silica gel column chromatography to obtain 199 mg of methyl 3-{2-[(tert-butoxycarbonyl)amino]propan-2-yl}benzoate.

Preparation Example 176

To 452 mg of methyl (1S)-1-{[(1S)-1-(4-methoxyphenyl)ethyl]amino}indane-5-carboxylate were added 34 ml of trifluoroacetic acid and 1.03 g of pentamethylbenzene, followed by stirring at 70° C. for 4 days, and the solvent was evaporated under reduced pressure. To the obtained residue were added a saturated aqueous sodium hydrogen carbonate solution and chloroform to carry out a layer separation operation. The organic layer was washed with saturated brine and dried over anhydrous magnesium sulfate, and the solvent was evaporated under reduced pressure. The obtained residue was purified by silica gel column chromatography to obtain 165 mg of methyl (1S)-1-aminoindane-5-carboxylate.

Preparation Example 178

To a mixed solution of 1.55 g of 1-methyl-3-(nitromethyl) benzene in 15 ml of ethanol and 6 ml of dioxane were added 0.05 ml of a 1 M aqueous sodium hydroxide solution and 1.89 ml of a 37% aqueous formalin solution, followed by stirring for 15 hours. 0.05 ml of a 1 M aqueous sodium hydroxide solution and 0.83 ml of a 37% aqueous formalin solution were added thereto, followed by stirring at 50° C. for 2 hours, and the solvent was evaporated under reduced pressure. To the obtained residue was added ethyl acetate, followed by washing with saturated brine and drying over anhydrous magnesium sulfate, and the solvent was evaporated under reduced pressure. The obtained residue was purified by silica gel column chromatography to obtain 1.91 g of 2-(3-methylphenyl)-2-nitropropane-1,3-diol.

Preparation Example 179

To a solution of 2 g of ethylpyridin-3-yl acetate in 40 ml of DMF were added 1.09 g of paraformaldehyde and 165 mg of sodium ethoxide, followed by stirring for 19 hours. Acetic acid was added thereto under ice-cooling and the solvent was evaporated under reduced pressure. The obtained residue was purified by silica gel column chromatography to obtain 1.29 g of ethyl 3-hydroxy-2-(hydroxymethyl)-2-(pyridin-3-yl)propanoate.

Preparation Example 180

To a mixture of 1.25 g of ethyl 3-hydroxy-2-(hydroxymethyl)-2-(pyridin-3-yl)propanoate in 13 ml of acetone were added 0.75 ml of 2,2-dimethoxypropane and 105 mg of p-toluenesulfonic acid monohydrate, followed by stirring for 12 hours. Then, 1.06 g of p-toluenesulfonic acid monohydrate was added thereto, followed by stirring for 6 hours. Further, 0.75 ml of 2,2-dimethoxypropane was added thereto, followed by stirring at 50° C. for 30 minutes, and the solvent was evaporated under reduced pressure. To the obtained residue were added 13 ml of acetone and 0.78 ml of 2-methoxy-1-propene at room temperature, followed by stirring for 30 minutes. To the reaction mixture were added a saturated aqueous sodium hydrogen carbonate solution and ethyl acetate to carry out a layer separation operation. The organic layer was washed with a saturated aqueous sodium hydrogen carbonate solution, water, and saturated brine in this order, and dried over anhydrous magnesium sulfate, and the solvent was evaporated under reduced pressure. The obtained residue was purified by silica gel column chromatography to obtain 1.16 g of ethyl 2,2-dimethyl-5-(pyridin-3-yl)-1,3-dioxane-5-carboxylate.

Preparation Example 181

To a mixed solution of 0.86 g of tert-butyl (1-phenylcyclopenta-3-en-1-yl)carbamate and 0.47 g of 4-methylmorpholine N-oxide in 22 ml of THF and 8.7 ml of water was added 0.42 ml of a 2.5% osmium tetraoxide/tert-butanol solution, followed by stirring for 2 hours and leaving to stand for 4 days. To the reaction mixture were added an aqueous sodium thiosulfate solution and ethyl acetate to carry out a layer separation operation. The organic layer was washed with saturated brine and dried over anhydrous magnesium sulfate, and the solvent was evaporated under reduced pressure. The obtained residue was purified by silica gel column chromatography to obtain 512 mg (Preparation Example 181a) and 126 mg (Preparation Example 181b), respectively, of tert-butyl [(3R,4S)-3,4-dihydroxy-1-phenylcyclopentyl]carbamate, as two kinds of single isomers, each having an undetermined configuration at the 1-position.

Preparation Example 182

A mixture of 620 mg of tert-butyl[(1R,2R)-2,3-dihydroxy-1-phenylpropyl]carbamate, 0.37 g of tert-butyldimethylchlorosilane, 0.19 g of imidazole, and 9.3 ml of dichloromethane was stirred for 2 hours. To the reaction mixture were added water and ethyl acetate to carry out a layer separation operation. The organic layer was washed with saturated brine and dried over anhydrous magnesium sulfate, and the solvent was evaporated under reduced pressure. The obtained residue was purified by silica gel column chromatography to obtain 705 mg of tert-butyl[(1R,2R)-3-{[tert-butyl(dimethyl)silyl]oxy}-2-hydroxy-1-phenylpropyl]carbamate.

Preparation Example 183

To 500 mg of methyl 6,6a-dihydro-1aH-indeno[1,2-b]oxirene-1a-carboxylate were added 860 mg of sodium azide, 309 mg of ammonium chloride, 4 ml of methanol, and 0.5 ml of water, followed by stirring at 80° C. for 2 hours. To the reaction mixture were added a saturated aqueous sodium hydrogen carbonate solution, water, and ethyl acetate to carry out a layer separation operation, and the organic layer was dried over anhydrous magnesium sulfate. To a solution of the obtained intermediate product in ethyl acetate-methanol was added 61 mg of 10% palladium-carbon (wet), followed by stirring for 6 hours under a hydrogen atmosphere. The reaction mixture was filtered over Celite and the solvent was then evaporated under reduced pressure to obtain 0.51 g of methyl rac-(1R,2R)-1-amino-2-hydroxyindane-1-carboxylate.

Preparation Example 184

To 1.09 g of 2,2-dimethyl-5-(pyridin-3-yl)-1,3-dioxane-5-carboxylic acid were added 20 ml of toluene, 0.9 ml of triethylamine, 2.4 ml of benzyl alcohol, and 1.3 ml of diphenylphosphoryl azide, followed by stirring at 100° C. for 17 hours. After leaving to be cooled, to the reaction mixture were added a saturated aqueous sodium hydrogen carbonate solution and ethyl acetate to carry out a layer separation operation. The organic layer was washed with saturated brine and dried over anhydrous magnesium sulfate, and the solvent was evaporated under reduced pressure. The obtained residue was purified by silica gel column chromatography to obtain 1.01 g of benzyl[2,2-dimethyl-5-(pyridin-3-yl)-1,3-dioxan-5-yl]carbamate.

Preparation Example 185

To a solution of 340 mg of sodium 2,2-dimethyl-5-(pyridin-2-yl)-1,3-dioxane-5-carboxylate in 5 ml of dioxane and 1 ml of water was added 0.21 ml of isobutyl chloroformate under ice-cooling, followed by stirring for 1 hour. A solution of 850 mg of sodium azide in 3 ml of water was added thereto, followed by stirring for 10 minutes under ice-cooling. To the reaction mixture were added water and diethyl ether to carry out a layer separation operation. The organic layer was washed with saturated brine and dried over anhydrous magnesium sulfate, and the solvent was evaporated under reduced pressure. To the obtained residue was added 5 ml of toluene, followed by stirring at 100° C. for 5 minutes. After leaving to be cooled, 0.7 ml of benzyl alcohol was added thereto at room temperature, followed by stirring at 100° C. for 19 hours. After leaving to be cooled, the solvent was evaporated under reduced pressure. The obtained residue was purified by silica gel column chromatography to obtain 223 mg of benzyl[2,2-dimethyl-5-(pyridin-2-yl)-1,3-dioxan-5-yl]carbamate.

Preparation Example 186

To a mixture of 1.6 g of 2,2-dimethyl-5-(3-methylphenyl)-5-nitro-1,3-dioxane in 24 ml of ethanol was added a suspension of a Raney nickel (manufactured by Aldrich, product obtained by washing 1 ml of an aqueous suspension with water and ethanol) in 9 ml of ethanol, followed by stirring for 22 hours under a hydrogen atmosphere at 4 atm. The reaction mixture was filtered over Celite and the solvent was then evaporated under reduced pressure. The obtained residue was purified by silica gel column chromatography to obtain 1.55 g of 2,2-dimethyl-5-(3-methylphenyl)-1,3-dioxan-5-amine.

Preparation Example 187

A suspension of 3.0 g of methyl 3-formylbenzoate, 2.25 g of (R)-2-methyl-2-propanesulfinamide, and 6.0 g of copper (II) sulfate in 50 ml of dichloromethane was stirred overnight. The reaction mixture was filtered over Celite and the solvent was then evaporated under reduced pressure. The obtained residue was purified by silica gel column chromatography to obtain 700 mg of methyl 3-[(E)-{[(R)-tert-butylsulfinyl]imino}methyl]benzoate.

Preparation Example 188

A suspension of 3.0 g of methyl 3-formylbenzoate, 2.5 g of (S)-2-methyl-2-propanesulfinamide, 250 mg of pyridinium paratoluene sulfonate, and 11 g of magnesium sulfate in 50 ml of dichloromethane was stirred overnight. The reaction mixture was filtered over Celite and the solvent was then evaporated under reduced pressure. The obtained residue was purified by silica gel column chromatography to obtain 3.0 g of methyl 3-[(E)-{[(S)-tert-butylsulfinyl]imino}methyl]benzoate.

Preparation Example 189

To a solution of 500 mg of methyl 3-[(E)-{[(S)-tert-butylsulfinyl]imino}methyl]benzoate in 12 ml of THF was added 0.50 ml of a 1 M diethylzinc/hexane solution at −78° C., followed by stirring at the same temperature for 5 minutes. 0.80 ml of a 3 M ethylmagnesium bromide/diethyl ether solution was added thereto at −78° C., followed by stirring at the same temperature for 2 hours. To the reaction mixture were added a saturated aqueous ammonium chloride solution and ethyl acetate to carry out a layer separation operation. The organic layer was washed with saturated brine and dried over anhydrous magnesium sulfate, and the solvent was evaporated under reduced pressure. The obtained residue was purified by silica gel column chromatography to obtain 447 mg of methyl 3-[(1S)-1-{[(S)-tert-butylsulfinyl]amino}propyl]benzoate.

Preparation Example 190

To a solution of 1 ml of diisopropylamine in 5 ml of THF was added 4.4 ml of a 1.6 M n-butyllithium/hexane solution under ice-cooling, followed by stirring at the same temperature for 15 minutes. 0.6 ml of methyl acetate was added thereto at −78° C., followed by stirring at the same temperature for 20 minutes. A solution of 3.6 g of chlorotitanium (IV) triisopropoxide in 7 ml of THF was added thereto, followed by stirring at the same temperature for 20 minutes. A solution of 500 mg of N-[(E)-(2,3-dimethylphenyl)methylene]-2-methylpropane-2-(R)-sulfinamide in 5 ml of THF was added thereto at −78° C., followed by stirring at the same temperature for 4 hours. To the reaction mixture were added a saturated aqueous ammonium chloride solution and ethyl acetate to carry out a layer separation operation. The organic layer was washed with saturated brine and dried over anhydrous magnesium sulfate, and the solvent was evaporated under reduced pressure. The obtained residue was purified by silica gel column chromatography to obtain 592 mg of methyl (3S)-3-{[(R)-tert-butylsulfinyl]amino}-3-(2,3-dimethylphenyl)propanoate.

Preparation Example 191

A suspension of 1 g of 2,2-dimethylspiro[1,3-dioxane-5,2'-inden]-1'(3'H)-one, 329 mg of hydroxylamine hydrochloride, and 388 mg of sodium acetate in 5 ml of ethanol was stirred for 12 hours. Then, 1.2 ml of triethylamine was added thereto, followed by stirring at room temperature for 3 days and further stirring at 50° C. for 1 hour. To the reaction mixture were added water and ethyl acetate to carry out a layer separation operation. The organic layer was washed with water and saturated brine, and dried over anhydrous magnesium sulfate, and the solvent was evaporated under reduced pressure. The obtained residue was purified by silica gel column chromatography to obtain 1.0 g of N-hydroxy-2,2-dimethylspiro[1,3-dioxane-5,2'-inden]-1'(3'H)-imine.

Preparation Example 192

To a suspension of 384 mg of lithium aluminum hydride in 22 ml of diethyl ether were added 0.5 g of N-hydroxy-2,2-dimethylspiro[1,3-dioxane-5,2'-inden]-1'(3'H)-imine and 5 ml of THF under ice-cooling, followed by stirring at 40° C. for 8 hours. 0.55 ml of water, 0.55 ml of a 15% aqueous sodium hydroxide solution, and 1.65 ml of water were added thereto under ice-cooling. After filtration through Celite, the solvent was evaporated under reduced pressure. The obtained residue was purified by silica gel column chromatography to obtain 146 mg of 2,2-dimethyl-1',3'-dihydrospiro[1,3-dioxane-5,2'-inden]-1'-amine.

Preparation Example 193

A mixture of 1 g of tert-butyl[(1S)-1-(3-bromophenyl)ethyl]carbamate, 18 mg of bis(tri-tert-butylphosphine)palladium (0), 180 mg of zinc fluoride, 1 ml of [(1-methoxy-2-methylpropa-1-en-1-yl)oxy](trimethyl)silane, and 10 ml of DMF was stirred at 80° C. overnight and at 100° C. for 5 hours. 25 mg of bis(tri-tert-butylphosphine)palladium (0) and 0.34 ml of [(1-methoxy-2-methylpropa-1-en-1-yl)oxy](trimethyl)silane were added thereto, followed by stirring at 80° C. for 3 days. To the reaction mixture were added water and ethyl acetate to carry out a layer separation operation. The organic layer was washed with water and dried over anhydrous magnesium sulfate, and the solvent was evaporated under reduced pressure. The obtained residue was purified by silica gel column chromatography to obtain 281 mg of methyl 2-(3-{(1S)-1-[(tert-butoxycarbonyl)amino]ethyl}phenyl)-2-methylpropanoate.

Preparation Example 194

To a solution of 130 mg of 2-(trimethylsilyl)ethyl rac-[(2R,3S)-2,3-dihydroxy-1-methyl-2,3-dihydro-1H-inden-1-yl]carbamate in 4 ml of THF was added 70 mg of 55% sodium hydride under ice-cooling, followed by stirring at the same temperature for 1 hour. To the reaction mixture were added a saturated aqueous ammonium chloride solution and ethyl acetate to carry out a layer separation operation, followed by drying over anhydrous magnesium sulfate, and the solvent was evaporated under reduced pressure. The obtained residue was purified by silica gel column chromatography to obtain 70 mg of 2-(trimethylsilyl)ethyl rac-[(1R,2S,3R)-2,3-dihydroxy-1-methyl-2,3-dihydro-1H-inden-1-yl]carbamate and 45 mg of rac-(3aR,8S,8aR)-8-hydroxy-3a-methyl-3,3a,8,8a-tetrahydro-2H-indeno[1,2-d][1,3]oxazol-2-one.

Preparation Example 195

To a solution of 3.4 g of 1-methyl-1H-indene in 136 ml of ether was added 16.2 ml of a 1.62 M n-butyllithium/hexane solution at −78° C., followed by stirring at room temperature for 30 minutes. To the reaction mixture were added 15.5 ml of tetra-iso-propyl titanate and 2.41 ml of methyl chloroformate at −78° C., followed by stirring at −78° C. for 2 hours. To the reaction mixture were added 1 M hydrochloric acid and ethyl acetate to carry out a layer separation operation, followed by drying over anhydrous magnesium sulfate, and the solvent was evaporated under reduced pressure. The obtained residue was purified by silica gel column chromatography to obtain 1.57 g of methyl 1-methyl-1H-indene-1-carboxylate.

Preparation Example 196

To a solution of 1.0 g of tert-butyl (3S)-piperidin-3-yl carbamate in 20 ml of DMF were added 0.77 ml of methyl 2-fluorobenzoate and 1.4 g of potassium carbonate, followed by stirring at 130° C. overnight. After leaving to be cooled, to the reaction mixture were added water and ethyl acetate to carry out a layer separation operation. The organic layer was washed with saturated brine and dried over anhydrous magnesium sulfate, and the solvent was evaporated under reduced pressure. The obtained residue was purified by silica gel column chromatography to obtain 590 mg of methyl 2-{(3S)-3-[(tert-butoxycarbonyl)amino]piperidin-1-yl}benzoate.

Preparation Example 197

To a solution of 280 mg of methyl 3-[(2S)-2-{[(1S)-1-phenylethyl]amino}propyl]benzoate in 6.8 ml of ethanol were added 30 mg of 20% palladium-carbon hydroxide (wet) and 320 mg of ammonium formate, followed by stirring at 80° C. for 4 hours. The reaction mixture was filtered over Celite and the solvent was then evaporated under reduced pressure. To the obtained residue were added a saturated aqueous sodium hydrogen carbonate solution and chloroform to carry out a layer separation operation, followed by drying over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure to obtain 180 mg of methyl 3-[(2S)-2-aminopropyl]benzoate.

Preparation Example 198

To a solution of 300 mg of tert-butyl[(1R,2S)-3-{[tert-butyl(dimethyl)silyl]oxy}-2-hydroxy-1-phenylpropyl]carbamate and 5 ml of methanol was added 5 ml of a 4 M hydrogen chloride/dioxane solution, followed by stirring for 2 hours. The solvent was evaporated under reduced pressure to obtain 171 mg of (2S,3R)-3-amino-3-phenylpropane-1,2-diol hydrochloride.

Preparation Example 199

To 448 mg of (2R,3R)-3-amino-3-phenylpropane-1,2-diol hydrochloride were added 18 ml of dichloromethane, 0.77 ml of triethylamine, and 0.53 g of di-tert-butyl dicarbonate, followed by stirring for 3 hours, and the solvent was evaporated under reduced pressure. The obtained residue was purified by silica gel column chromatography to obtain 620 mg of tert-butyl[(1R,2R)-2,3-dihydroxy-1-phenylpropyl]carbamate.

Preparation Example 200

To a solution of 300 mg of N-[(2E)-1-{[tert-butyl(dimethyl)silyl]oxy}propan-2-ylidene]-2-methylpropane-2-(S)-sulfinamide in 2 ml of toluene was added 0.62 ml of a 2.0 M trimethylaluminum/toluene solution at −78° C., followed by stirring for 30 minutes. Further, 3.2 ml of a 0.5 Methyllithium/benzene-cyclohexane solution was added thereto at −78° C., followed by stirring for 1 hour. To the reaction mixture were added a saturated aqueous ammonium chloride solution and ethyl acetate to carry out a layer separation operation. The organic layer was washed with saturated brine and dried over anhydrous magnesium sulfate, and the solvent was evaporated under reduced pressure. The obtained residue was purified by silica gel column chromatography to obtain 160 mg of N-[(2R)-1-{[tert-butyl(dimethyl)silyl]oxy}-2-methylbutan-2-yl]-2-methylpropane-2-(S)-sulfinamide.

Preparation Example 201

To a solution of 97 mg of N-[(2R)-1-{[tert-butyl(dimethyl)silyl]oxy}-2-methylbutan-2-yl]-2-methylpropane-2-(S)-sulfinamide in 1 ml of methanol was added 1.3 ml of a 4 M hydrogen chloride/dioxane solution, followed by stirring for 2 hours. The solvent was evaporated under reduced pressure to obtain 63 mg of (2R)-2-amino-2-methylbutan-1-ol hydrochloride.

Preparation Example 239

Preparation was carried out using the compound of Preparation Example 168a by the same method as in Preparation Example 171 as described above.

Preparation Example 240

Preparation was carried out using the compound of Preparation Example 239 by the same method as in Preparation Example 172 as described above.

Preparation Example 278

Preparation was carried out using the compound of Preparation Example 181a by the same method as in Example 5 as described below.

Preparation Example 279

Preparation was carried out using the compound of Preparation Example 181b by the same method as in Example 5 as described below.

Hereinafter, Preparation Examples for the compounds of the formula (I) of the present invention are shown as Examples. Further, for the respective Example Compounds, the structures are shown in Tables 32 to 99, and the physicochemical data and preparation methods are shown in Tables 100 to 131. Since the compounds of Examples 36 to 660, 662, 664 to 668, 670 to 672, 675 to 682, 686 to 692, 694, 696 to 697, 700 to 701, 706 to 708, and 715 to 757, 760 to 765, 768 to 796 and 799 to 885 were prepared in the same manner as the methods of Examples 1 to 35, 661, 663 and 709 to 714, they are described only in Tables as described later.

Example 1

To a solution of 600 mg of 8-(cyclohexylmethoxy)-2-methylimidazo[1,2-a]pyridine-3-carboxylic acid in 10 ml of DMF were added 500 mg of tert-butyl (3S)-3-aminopiperidine-1-carboxylate, 518 mg of N-[3-(dimethylamino)propyl]-N'-ethylcarbodiimide hydrochloride, and 366 mg of 1-hydroxybenzotriazole, followed by stirring overnight. To the reaction mixture were added water and ethyl acetate to carry out a layer separation operation. The organic layer was washed with water and saturated brine, dried over anhydrous sodium sulfate, and the solvent was evaporated under reduced pressure. The obtained residue was purified by silica gel column chromatography to obtain 808 mg of tert-butyl (3S)-3-({[8-(cyclohexylmethoxy)-2-methylimidazo[1,2-a]pyridin-3-yl]carbonyl}amino)piperidine-1-carboxylate.

Example 2

A mixture of 120 mg of N-[(1R)-2-{[tert-butyl(dimethyl)silyl]oxy}-1-phenylethyl]-8-hydroxy-2-methylimidazo[1,2-a]pyridine-3-carboxamide, 60 μl of cyclopentylmethanol, 156 μl of (tributylphosphoranylidene)acetonitrile, and 2.4 ml of toluene was stirred at 110° C. for 16 hours, followed by purification using silica gel chromatography, to obtain 100 mg of N-[(1R)-2-{[tert-butyl(dimethyl)silyl]oxy}-1-phenylethyl]-8-(cyclopentylmethoxy)-2-methylimidazo[1,2-a]pyridine-3-carboxamide.

Example 3

To a solution of 370 mg of ethyl 3-{[(1R)-2-{[tert-butyl(dimethyl)silyl]oxy}-1-phenylethyl]carbamoyl}-8-[(2-fluorobenzyl)oxy]-2-methylimidazo[1,2-a]pyridine-6-carboxylate in 12 ml of THF was added 1.22 ml of a 1 M tetrabutylammonium fluoride/THF solution, followed by stirring for 30 minutes. To the reaction mixture were added water and ethyl acetate to carry out a layer separation operation. The organic layer was dried over anhydrous magnesium sulfate and the solvent was evaporated under reduced pressure. The obtained residue was purified by silica gel column chromatography to obtain 220 mg of ethyl 8-[(2-fluorobenzyl)oxy]-3-{[(1R)-2-hydroxy-1-phenylethyl]carbamoyl}-2-methylimidazo[1,2-a]pyridine-6-carboxylate.

Example 4

To a solution of 90 mg of 6-bromo-8-(cyclohexylmethoxy)-N-[(1R)-2-hydroxy-1-phenylethyl]-2-methylimidazo[1,2-a]pyridine-3-carboxamide in 1.8 ml of N-methyl-2-pyrrolidone were added 54 mg of zinc cyanide and 27 mg of [1,1-bis(diphenylphosphino)ferrocene]dichloropalladium (II), followed by stirring at 180° C. for 30 minutes under a condition for microwave irradiation. To the reaction mixture was added 46 mg of zinc cyanide, followed by further stirring at 180° C. for 30 minutes under a condition for microwave irradiation. To the reaction mixture were added ethyl acetate and a saturated aqueous sodium hydrogen carbonate solution, followed by filtration through Celite. A layer separation operation of the obtained filtrate was carried out, the organic layer was washed with a saturated aqueous sodium hydrogen carbonate solution and saturated brine, and dried over anhydrous sodium sulfate, and the solvent was evaporated under reduced pressure. The obtained residue was purified by silica gel column chromatography to obtain 7 mg of 6-cyano-8-(cyclohexylmethoxy)-N-[(1R)-2-hydroxy-1-phenylethyl]-2-methylimidazo[1,2-a]pyridine-3-carboxamide.

Example 5

To a solution of 1.44 g of tert-butyl 4-({[8-(cyclohexylmethoxy)-2-methylimidazo[1,2-a]pyridin-3-yl]carbonyl}amino)piperidine-1-carboxylate in 15 ml of ethyl acetate was added 3.8 ml of a 4 M hydrogen chloride/ethyl acetate solution, followed by stirring for 1 day. The reaction mixture was concentrated under reduced pressure, and to the obtained residue were added ethyl acetate and ethanol. The resulting solid was collected by filtration and dried to obtain 1.29 g of 8-(cyclohexylmethoxy)-2-methyl-N-(piperidin-4-yl)imidazo[1,2-a]pyridine-3-carboxamide dihydrochloride.

Example 6

To a suspension of 400 mg of 8-(cyclohexylmethoxy)-2-methyl-N-[(3S)-pyrrolidin-3-yl]imidazo[1,2-a]pyridine-3-carboxamide dihydrochloride, 0.26 ml of triethylamine, and 0.23 ml of a 37% aqueous formaldehyde solution in 11 ml of dichloroethane was added 592 mg of sodium triacetoxyborohydride under ice-cooling, followed by stirring at room temperature for 1 hour. To the reaction mixture were added a saturated aqueous sodium hydrogen carbonate solution and chloroform to carry out a layer separation operation. The organic layer was dried over anhydrous sodium sulfate and the solvent was evaporated under reduced pressure. The obtained residue was purified by silica gel column chromatography to obtain 249 mg of 8-(cyclohexylmethoxy)-2-methyl-N-[(3S)-1-methylpyrrolidin-3-yl]imidazo[1,2-a]pyridine-3-carboxamide.

Example 7

To a suspension of 307 mg of 8-(cyclohexylmethoxy)-2-methyl-N-[(3S)-piperidin-3-yl]imidazo[1,2-a]pyridine-3-carboxamide dihydrochloride, 335 mg of potassium carbonate, 5 ml of acetonitrile, and 5 ml of DMF was added 92 μl of bromoethyl acetate under ice-cooling, followed by stirring for 3 hours under ice-cooling. To the reaction mixture were added water and chloroform to carry out a layer separation operation. The organic layer was dried over anhydrous sodium sulfate and the solvent was evaporated under reduced pressure. The obtained residue was purified by silica gel column chromatography to obtain 299 mg of ethyl[(3S)-3-({[8-(cyclohexylmethoxy)-2-methylimidazo[1,2-a]pyridin-3-yl]carbonyl}amino)piperidin-1-yl]acetate.

Example 8

To a mixture of 150 mg of methyl 4-[({[8-(cyclohexylmethoxy)-2-methylimidazo[1,2-a]pyridin-3-yl]carbonyl}amino)methyl]piperidine-4-carboxylate dihydrochloride, 150 μl of triethylamine, and 5 ml of dichloromethane was added 25 μl of acetyl chloride under ice-cooling, followed by stirring at room temperature for 2 hours. To the reaction mixture were added water and ethyl acetate to carry out a layer separation operation. The organic layer was washed with saturated brine and dried over anhydrous magnesium sulfate, and the solvent was evaporated under reduced pressure. The obtained residue was purified by silica gel column chromatography to obtain 135 mg of methyl 1-acetyl-4-[({[8-(cyclohexylmethoxy)-2-methylimidazo[1,2-a]pyridin-3-yl]carbonyl}amino)methyl]piperidine-4-carboxylate.

Example 9

To a mixture of 150 mg of methyl 4-[({[8-(cyclohexylmethoxy)-2-methylimidazo[1,2-a]pyridin-3-yl]carbonyl}amino)methyl]piperidine-4-carboxylate dihydrochloride, 150 μl of triethylamine, and 5 ml of dichloromethane was added 35 μl of methanesulfonyl chloride under ice-cooling, followed by stirring at room temperature for 2 hours. To the reaction mixture were added water and ethyl acetate to carry out a layer separation operation. The organic layer was washed with saturated brine and dried over anhydrous magnesium sulfate, and the solvent was evaporated under reduced pressure. The obtained residue was purified by silica gel column chromatography to obtain 85 mg of methyl 4-[({[8-(cyclohexylmethoxy)-2-methylimidazo[1,2-a]pyridin-3-yl]carbonyl}amino)methyl]-1-(methylsulfonyl)piperidine-4-carboxylate.

Example 10

To a solution of 200 mg of 8-(cyclohexylmethoxy)-2-methyl-N-[(3S)-piperidin-3-yl]imidazo[1,2-a]pyridine-3-carboxamide dihydrochloride in 5 ml of isopropylalcohol were added 220 μl of triethylamine and 72 μl of (trimethylsilyl)isocyanate, followed by stirring for 6 hours. To the reaction mixture were added water and ethyl acetate to carry out a layer separation operation. The organic layer was washed with water, a saturated aqueous sodium hydrogen carbonate solution, and saturated brine in this order, and dried over anhydrous sodium sulfate, the solvent was evaporated under reduced pressure, and the obtained residue was purified by silica gel column chromatography. The obtained solid was suspended in ethyl acetate, and 120 μl of 4 M hydrogen chloride/ethyl acetate solution was added thereto, followed by stirring. The resulting solid was collected by filtration and dried to obtain 170 mg of N-[(3S)-1-carbamoylpiperidin-3-yl]-8-(cyclohexylmethoxy)-2-methylimidazo[1,2-a]pyridine-3-carboxamide hydrochloride.

Example 11

To 200 mg of 8-(cyclohexylmethoxy)-2-methyl-N-[(3S)-piperidin-3-yl]imidazo[1,2-a]pyridine-3-carboxamide dihydrochloride were added 5 ml of pyridine and 217 mg of sulfamide, followed by heating to reflux for 4 hours. After leaving to be cooled at room temperature, to the reaction mixture were added water and chloroform to carry out a layer separation operation. The organic layer was dried over anhydrous sodium sulfate, the solvent was evaporated under reduced pressure, and the obtained residue was purified by silica gel column chromatography. The obtained solid was suspended in ethyl acetate, and 120 μl of a 4 M hydrogen chloride/ethyl acetate solution was added thereto. The resulting solid was collected by filtration and dried to obtain 151 mg of N-[(3S)-1-(aminosulfonyl)piperidin-3-yl]-8-(cyclohexylmethoxy)-2-methylimidazo[1,2-a]pyridine-3-carboxamide hydrochloride.

Example 12

To a solution of 216 mg of tert-butyl (3R)-3-({[8-(cyclohexylmethoxy)-2-methylimidazo[1,2-a]pyridin-3-yl]carbonyl}amino)-5-methylhexanoate in 2 ml of dichloromethane was added 2 ml of trifluoroacetic acid, followed by stirring overnight. The solvent was evaporated under reduced pressure, and water, a saturated aqueous sodium hydrogen carbonate solution, 1 M hydrochloric acid, and chloroform were added thereto to carry out a layer separation operation. The organic layer was dried over anhydrous sodium sulfate, the solvent was evaporated under reduced pressure, and the obtained residue was purified by silica gel column chromatography. To the obtained purified product were added ethyl acetate and diisopropyl ether, and the resulting solid was collected by filtration and dried to obtain 147 mg of (3R)-3-({[8-(cyclohexylmethoxy)-2-methylimidazo[1,2-a]pyridin-3-yl]carbonyl}amino)-5-methylhexanoic acid.

Example 13

To a solution of 290 mg of 8-(cyclohexylmethoxy)-N-[(1S)-1-(2-fluorophenyl)-3-hydroxypropyl]-2-methylimidazo[1,2-a]pyridine-3-carboxamide in dichloromethane was added 300 mg of 1,1,1-triacetoxy-1,1-dihydro-1,2-benziodoxol-3(1H)-one, followed by stirring overnight. To the reaction mixture were added saturated aqueous sodium bicarbonate, an aqueous sodium thiosulfate solution, and ethyl acetate to carry out a layer separation operation. The organic layer was washed with saturated aqueous sodium bicarbonate and dried over anhydrous magnesium sulfate, and the solvent was evaporated under reduced pressure. To a solution of the obtained residue and 230 μl of 2-methyl-2-butene in 6.5 ml of dioxane was added 1.7 ml of an aqueous solution of 93 mg of sodium chlorite and 315 mg of sodium dihydrogen phosphate in a water bath, followed by stirring for 30 minutes in a water bath. To the reaction mixture were added water, 1 M hydrochloric acid, and chloroform to carry out a layer separation operation. The organic layer was dried over anhydrous magnesium sulfate, the solvent was evaporated under reduced pressure, and the obtained residue was purified by silica gel column chromatography. To the obtained purified product was added diisopropyl ether, and the resulting solid was filtered and dried to obtain 80 mg of (3S)-3-({[8-(cyclohexylmethoxy)-2-methylimidazo[1,2-a]pyridin-3-yl]carbonyl}amino)-3-(2-fluorophenyl)propanoic acid.

Example 14

To a suspension of 20 mg of lithium aluminum hydride in 5 ml of THF was added a solution of 220 mg of methyl (2R)-2-({[8-(cyclohexylmethoxy)-2-methylimidazo[1,2-a]pyridin-3-yl]carbonyl}amino)-3-(2-methylphenyl)propanoate in 2 ml of THF under ice-cooling, followed by stirring for 7 hours under ice-cooling. To the reaction mixture was added 180 mg of sodium sulfate decahydrate, followed by stirring for a while. The reaction mixture was filtered over Celite, the solvent was then evaporated under reduced pressure, and the obtained residue was purified by silica gel column chromatography. The obtained purified product was dissolved in ethyl acetate and a 4 M hydrogen chloride/ethyl acetate solution was added thereto. The solvent was evaporated under reduced pressure, and then diisopropyl ether was added thereto, followed by stirring. The resulting solid was collected by filtration and dried to obtain 72 mg of 8-(cyclohexylmethoxy)-N-[(1R)-2-hydroxy-1-(2-methylbenzyl)ethyl]-2-methylimidazo[1,2-a]pyridine-3-carboxamide hydrochloride.

Example 15

To a solution of 185 mg of methyl (2E,4S)-4-({[8-(cyclohexylmethoxy)-2-methylimidazo[1,2-a]pyridin-3-yl]carbonyl}amino)-4-phenylbuta-2-enoate in 3.7 ml of ethyl acetate was added 20 mg of 10% palladium-carbon, followed by stirring for 8 hours under a hydrogen atmosphere. The reaction mixture was filtered over Celite and the solvent was evaporated under reduced pressure to obtain 165 mg of methyl (4S)-4-({[8-(cyclohexylmethoxy)-2-methylimidazo[1,2-a]pyridin-3-yl]carbonyl}amino)-4-phenylbutanoate.

Example 16

To 245 mg of 8-(cyclohexylmethoxy)-2-methyl-N-[(3S)-1-methylpyrrolidin-3-yl]imidazo[1,2-a]pyridine-3-carboxamide were added 12 ml of ethyl acetate and 364 μl of a 4 M hydrogen chloride/ethyl acetate solution, followed by stirring. The resulting solid was collected by filtration and dried to obtain 258 mg of 8-(cyclohexylmethoxy)-2-methyl-N-[(3S)-1-methylpyrrolidin-3-yl]imidazo[1,2-a]pyridine-3-carboxamide hydrochloride.

Example 17

To a solution of 280 mg of ethyl 8-[(2-fluorobenzyl)oxy]-2-methylimidazo[1,2-a]pyridine-6-carboxylate, 208 mg of 4-(dimethylamino)pyridine, and 5 ml of chloroform was added 191 μl of trichloroacetyl chloride under ice-cooling, followed by stirring at room temperature for 1 hour and at 65° C. overnight. After leaving to be cooled at room temperature, the solvent was evaporated under reduced pressure, and to the obtained residue were added acetonitrile and 429 mg of (1R)-2-{[tert-butyl(dimethyl)silyl]oxy}-1-phenylethanamine, followed by stirring overnight. To the reaction mixture were added water and chloroform to carry out a layer separation operation. The organic layer was dried over anhydrous sodium sulfate and the solvent was evaporated under reduced pressure. The obtained residue was purified by silica gel column chromatography to obtain 370 mg of ethyl 3-{[(1R)-2-{[tert-butyl(dimethyl)silyl]oxy}-1-phenyl ethyl]carbamoyl}-8-[(2-fluorobenzyl)oxy]-2-methylimidazo[1,2-a]pyridine-6-carboxylate.

Example 18

To a mixture of 100 mg of 8-[(2-fluorobenzyl)oxy]-3-{[(1R)-2-hydroxy-1-phenylethyl]carbamoyl}-2-methylimidazo[1,2-a]pyridine-6-carboxylic acid, 28 μl of 4-methylmorpholine, and 0.7 ml of dimethoxyethane was added 34 μl of isobutyl chloroformate under ice-cooling, followed by stirring at room temperature overnight. The insoluble material was removed by filtration, and then to the filtrate were added 16 mg of sodium borohydride and 210 μl of methanol under ice-cooling, followed by stirring for 30 minutes under ice-cooling. To the reaction mixture were added a saturated aqueous ammonium chloride solution and chloroform to carry out a layer separation operation. The organic layer was dried over anhydrous magnesium sulfate and the solvent was evaporated under reduced pressure. The obtained residue was purified by silica gel column chromatography to obtain 21 mg of 8-[(2-fluorobenzyl)oxy]-6-(hydroxymethyl)-N-[(1R)-2-hydroxy-1-phenylethyl]-2-methylimidazo[1,2-a]pyridine-3-carboxamide.

Example 19

To a suspension of 300 mg of 8-(cyclohexylmethoxy)-N-[(1R)-2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)-1-phenylethyl]-2-methylimidazo[1,2-a]pyridine-3-carboxamide in 6 ml of ethanol was added 0.13 ml of hydrazine monohydrate, followed by stirring at 85° C. for 1 hour. The solvent was evaporated under reduced pressure and the obtained residue was purified by silica gel column chromatography to obtain 200 mg of N-[(1R)-2-amino-1-phenylethyl]-8-(cyclohexylmethoxy)-2-methylimidazo[1,2-a]pyridine-3-carboxamide.

Example 20

To a solution of 1.2 g of benzyl 4-({[8-(cyclohexylmethoxy)-2-methylimidazo[1,2-a]pyridin-3-yl]carbonyl}amino)-4-(2-methoxy-2-oxoethyl)piperidine-1-carboxylate in 30 ml of methanol was added 300 mg of 10% palladium-carbon, followed by stirring overnight under a hydrogen atmosphere. The reaction mixture was filtered over Celite and the solvent was then evaporated under reduced pressure to obtain 900 mg of methyl[4-({[8-(cyclohexylmethoxy)-2-methylimidazo[1,2-a]pyridin-3-yl]carbonyl}amino)piperidin-4-yl]acetate.

Example 21

To a suspension of 300 mg of 8-(cyclohexylmethoxy)-2-methylimidazo[1,2-a]pyridine-3-carboxylic acid in 5 ml of THF was added 253 mg of 1,1'-carbonyldiimidazole, followed by stirring at 60° C. for 1 hour. Subsequently, 283 mg of 3-(aminosulfonyl)propyl acetate and 389 μl of 1,8-diazabicyclo[5.4.0]-7-undecene were added thereto under ice-cooling, followed by stirring at room temperature overnight. To the reaction mixture were added water and ethyl acetate to carry out a layer separation operation. The organic layer was washed with saturated brine and dried over anhydrous sodium sulfate, the solvent was evaporated under reduced pressure, and the obtained residue was purified by silica gel column chromatography. Since the reaction was not completed, to the obtained purified product were added again 57 mg of 3-(aminosulfonyl)propyl acetate, 60 mg of N-[3-(dimethylamino)propyl]-N'-ethylcarbodiimide hydrochloride, 38 mg of 4-(dimethylamino)pyridine, and 2 ml of DMF, followed by stirring at room temperature overnight. To the reaction mixture were added a saturated aqueous ammonium chloride solution and chloroform to carry out a layer separation operation. The organic layer was dried over anhydrous sodium sulfate, the solvent was evaporated under reduced pressure, and the obtained residue was purified by silica gel column chromatography. To the obtained product were added ethyl acetate and ethanol, followed by stirring. The resulting solid was collected by filtration and dried to obtain 149 mg of 3-[({[8-(cyclohexylmethoxy)-2-methylimidazo[1,2-a]pyridin-3-yl]carbonyl}amino)sulfonyl]propyl acetate.

Example 22

To 130 mg of 3-[({[8-(cyclohexylmethoxy)-2-methylimidazo[1,2-a]pyridin-3-yl]carbonyl}amino)sulfonyl]propyl acetate were added 2 ml of methanol, 2 ml of THF, and 1 ml of a 1 M aqueous sodium hydroxide solution, followed by stirring for 8.5 hours. The solvent was evaporated under reduced pressure and to the obtained residue were added water and 1 M hydrochloric acid. The solvent was evaporated under reduced pressure and the obtained residue was purified by silica gel column chromatography. To the obtained purified product were added ethyl acetate and hexane, followed by stirring. The resulting solid was collected by filtration and dried to obtain 41 mg of 8-(cyclohexylmethoxy)-N-[(3-hydroxypropyl)sulfonyl]-2-methylimidazo[1,2-a]pyridine-3-carboxamide.

Example 23

To a mixture of 8.7 mg of 8-(cyclohexylmethoxy)-2-methylimidazo[1,2-a]pyridine-3-carboxylic acid, 5.1 mg of cyclopropylamine, 4.1 mg of 1-hydroxybenzotriazole, 1 ml of DMF, and 28 μl of diisopropylethylamine was added 50 mg of polystyrene N-cyclohexylcarbodiimide-N'-propyloxymethyl (PS-Carbodiimide manufactured by Biotage), followed by stirring at room temperature for 16 hours. Subsequently, 1 ml of DMF, 50 mg of macroporious triethylammonium methylpolystyrene carbonate (MP-Carbonate manufactured by Biotage) and 50 mg of polystyrene methyl isocyanate (PS-Isocyanate manufactured by Biotage), followed by stirring at room temperature for 3 hours. The resin of the reaction mixture was removed by filtration and the filtrate was concentrated under reduced pressure. The obtained residue was purified by preparative HPLC (high performance liquid chromatography) to obtain 8.7 mg of 8-(cyclohexylmethoxy)-N-cyclopropyl-2-methylimidazo[1,2-a]pyridine-3-carboxamide.

Example 24

To a mixture of 5.8 mg of 8-(cyclohexylmethoxy)-2-methylimidazo[1,2-a]pyridine-3-carboxylic acid, 6.1 mg of (S)-(+)-2-phenylglycine methyl ester hydrochloride, 2.7 mg of 1-hydroxybenzotriazole, 700 μl of DMF, and 19 μl of diisopropylethylamine was added 50 mg of polystyrene N-cyclohexylcarbodiimide-N'-propyloxymethyl (PS-Carbodiimide manufactured by Biotage), followed by stirring at room temperature for 20 hours. Subsequently, 50 mg of macroporous triethylammonium methylpolystyrene carbonate (MP-Carbonate manufactured by Biotage) and 50 mg of polystyrene methyl isocyanate (PS-Isocyanate manufactured by Biotage) were added thereto, followed by stirring at room temperature for 2 hours. The resin was removed by filtration, the filtrate was concentrated under reduced pressure, and to the obtained residue were added 100 μl of THF, 200 μl of methanol, and 50 μl of a 1 M aqueous sodium hydroxide solution, followed by stirring at 50° C. for 20 hours. To the reaction mixture that had been left to be cooled to room temperature were added 0.5 ml of water and 50 μl of 1 M hydrochloric acid, followed by concentration under reduced pressure. The obtained residue was purified by preparative HPLC to obtain 6.7 mg of (2S)-({[8-(cyclohexylmethoxy)-2-methylimidazo[1,2-a]pyridin-3-yl]carbonyl}amino)(phenyl)acetic acid.

Example 25

To a mixture of 5.8 mg of 8-(cyclohexylmethoxy)-2-methylimidazo[1,2-a]pyridine-3-carboxylic acid, 7.1 mg of tert-butyl (3R)-3-amino-4-phenylbutanoate, 2.7 mg of 1-hydroxybenzotriazole, 700 μl of DMF, and 19 μl of diisopropylethylamine was added 50 mg of polystyrene N-cyclohexylcarbodiimide-N'-propyloxymethyl (PS-Carbodiimide manufactured by Biotage), followed by stirring at room temperature for 20 hours. To the reaction mixture were added 50 mg of macroporous triethylammonium methylpolystyrene carbonate (MP-Carbonate manufactured by Biotage) and 50 mg of polystyrene methyl isocyanate (PS-Isocyanate manufactured by Biotage), followed by stirring at room temperature for 2 hours. The resin was removed by filtration, the filtrate was concentrated under reduced pressure, and to the obtained residue were added 100 μl of 1,4-dioxane and 200 μl of a 4 M hydrogen chloride/1,4-dioxane solution, followed by stirring at room temperature for 20 hours. The reaction mixture was concentrated under reduced pressure and the obtained residue was purified by preparative HPLC to obtain 5.6 mg of (3R)-3-({[8-(cyclohexylmethoxy)-2-methylimidazo[1,2-a]pyridin-3-yl]carbonyl}amino)-4-phenylbutanoic acid.

Example 26

A mixture of 8.5 mg of N-[(1R)-2-{[tert-butyl(dimethyl)silyl]oxy}-1-phenylethyl]-8-hydroxy-2-methylimidazo[1,2-a]pyridine-3-carboxamide, 5.6 mg of α-bromo-2,5-difluorotoluene, 5.0 mg of potassium carbonate, and 700 μl of DMF was stirred at 30° C. for 28 hours. To the reaction mixture were added 1 ml of water, 0.5 ml of saturated brine, and 4 ml of chloroform to carry out a layer separation operation. The organic layer was concentrated under reduced pressure, and to the residue were added 300 μl of THF and 300 μl of 1 M hydrochloric acid, followed by stirring at room temperature for 6 hours. To the reaction mixture were added 300 μl of a 1 M aqueous sodium hydroxide solution and 100 of saturated aqueous sodium bicarbonate, followed by extraction with 3 ml of chloroform. The solvent was evaporated under reduced pressure and the obtained residue was purified by preparative HPLC to obtain 6.3 mg of 8-[(2,5-difluorobenzyl)oxy]-N-[(1R)-2-hydroxy-1-phenylethyl]-2-methylimidazo[1,2-a]pyridine-3-carboxamide.

Example 27

To a solution of 250 mg of 8-(cyclohexylmethoxy)-2-methyl-N-[(3S)-piperidin-3-yl]imidazo[1,2-a]pyridine-3-carboxamide dihydrochloride in 10 ml of methanol were added 157 μl of triethylamine, 300 mg of Molecular Sieves 3A, 323 μl of acetic acid, 1.53 ml of [(1-ethoxy cyclopropyl)oxy](trimethyl)silane, and 146 mg of sodium cyanoborohydride under ice-cooling, followed by stirring for 6 hours under heating to reflux. The insoluble material was removed by filtration and the filtrate was concentrated under reduced pressure. To the obtained residue were added saturated aqueous sodium bicarbonate and chloroform to carry out a layer separation operation. The organic layer was dried over anhydrous sodium sulfate, the solvent was evaporated under reduced pressure, and the obtained residue was purified by silica gel column chromatography. To a mixture of the obtained purified product, ethyl acetate, and methanol was added a 4 M hydrogen chloride/ethyl acetate solution under ice-cooling, and the solvent was evaporated under reduced pressure. To the obtained residue was added ethyl acetate and hexane, followed by stirring. The resulting solid was collected by filtration and dried to obtain 136 mg of 8-(cyclohexylmethoxy)-N-[(3S)-1-cyclopropylpiperidin-3-yl]-2-methylimidazo[1,2-a]pyridine-3-carboxamide dihydrochloride.

Example 28

To a solution of 200 mg of 8-(cyclohexylmethoxy)-2-methyl-N-[(1R)-2-{methyl[(2-nitrophenyl)sulfonyl]amino}-1-phenylethyl]imidazo[1,2-a]pyridine-3-carboxamide in 3 ml of DMF were added 140 mg of potassium carbonate and 50 mg of 4-methylbenzenethiol, followed by stirring for 3 hours. To the reaction mixture were added water and chloroform/methanol (9/1) to carry out a layer separation operation. The organic layer was washed with saturated brine and dried over anhydrous magnesium sulfate, and the solvent was evaporated under reduced pressure. The obtained residue was purified by silica gel column chromatography to obtain 80 mg of 8-(cyclohexylmethoxy)-2-methyl-N-[(1R)-2-(methylamino)-1-phenylethyl]imidazo[1,2-a]pyridine-3-carboxamide.

Example 29

To a solution of 150 mg of methyl (2S,4S)-4-({[8-(cyclohexylmethoxy)-2-methylimidazo[1,2-a]pyridin-3-yl]carbonyl}amino)-1-methylpyrrolidine-2-carboxylate and 4 ml of dichloromethane was added dropwise 1.5 ml of a 1 M diisobutylaluminum hydride/toluene solution under ice-cooling, followed by stirring for 2 hours under ice-cooling. Subsequently, 1 M hydrochloric acid was added thereto, the reaction mixture was filtered over Celite, and to the filtrate were added ethyl acetate to carry out a layer separation operation. The organic layer was washed with water and saturated brine, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure and the obtained residue was purified by silica gel column chromatography. To a solution of the obtained purified product in ethyl acetate was added a hydrogen chloride/ethyl acetate solution, and the resulting solid was collected by filtration and dried to obtain 25 mg of 8-(cyclohexylmethoxy)-N-[(3S,5S)-5-(hydroxymethyl)-1-methylpyrrolidin-3-yl]-2-methylimidazo[1,2-a]pyridine-3-carboxamide dihydrochloride.

Example 30

To a solution of 32 mg of N-[(6-chloropyridin-3-yl)methyl]-8-(cyclohexylmethoxy)-2-methylimidazo[1,2-a]pyridine-3-carboxamide in 0.6 ml of N-methyl-2-pyrrolidone was added 0.05 ml of ethyl piperidine-4-carboxylate to carry out a reaction at 150° C. for 30 minutes and further at 200° C. for 30 minutes under microwave irradiation. 24 mg of potassium carbonate was added thereto to carry out a reaction at 240° C. for 2 hours under microwave irradiation. To the reaction mixture were added a saturated aqueous ammonium chloride solution and ethyl acetate to carry out a layer separation operation. The organic layer was washed with water and saturated brine, and dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure and the obtained residue was purified by silica gel column chromatography. To the obtained purified product were added hexane and isopropyl ether, and the resulting solid was collected by filtration and dried to obtain 14 mg of 1-{4-[({[8-(cyclohexylmethoxy)-2-methylimidazo[1,2-a]pyridin-3-yl]carbonyl}amino)methyl]pyridin-2-yl}piperidine-4-carboxylic acid.

Example 31

To a solution of 70 mg of N-[(6-chloropyridin-3-yl)methyl]-8-(cyclohexylmethoxy)-2-methylimidazolo[1,2-a]pyridine-3-carboxamide in 1 mL of N-methyl-2-pyrrolidone was added 0.12 mL of ethyl piperidine-3-carboxylate to carry out a reaction at 240° C. for 50 minutes under microwave irradiation. To the reaction mixture were added a saturated aqueous ammonium chloride solution and ethyl acetate to carry out a layer separation operation. The organic layer was washed with saturated brine and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure and the obtained residue was purified by silica gel column chromatography to obtain 43 mg of ethyl 1-{5-[({[8-(cyclohexylmethoxy)-2-methylimidazolo[1,2-a]pyridin-3-yl]carbonyl}amino)methyl]pyridin-2-yl}piperidine-3-carboxylate.

Example 32

To a solution of 270 mg of methyl N-{[8-(cyclohexylmethoxy)-2-methylimidazo[1,2-a]pyridin-3-yl]carbonyl}serinate in 7 mL of methanol were added 210 mg of bisguanidine and 115 mg of sodium methoxide, followed by stirring at 65° C. for 8 hours. After leaving to be cooled, the insoluble material was collected by filtration, and washed with methanol, water, and hexane in this order to obtain 75 mg of 8-(cyclohexylmethoxy)-N-[1-(4,6-diamino-1,3,5-triazin-2-yl)-2-hydroxyethyl]-2-methylimidazo[1,2-a]pyridine-3-carboxamide.

Example 33

A mixture of 860 mg of 8-(cyclohexylmethoxy)-2-methylimidazo[1,2-a]pyridine-3-carboxylic acid, 992 mg of 1-benzyl-4-methylpiperidine-4-amine dihydrochloride, 170 mg of O-(7-azabenzotriazole-1-yl)-N,N,N',N',-tetramethyluronium hexafluorophosphate, 3 mL of diisopropylethylamine, and 10 mL of DMF was stirred for 1 day. To the reaction mixture were added water and ethyl acetate to carry out a layer separation operation. The organic layer was washed with water and saturated brine in this order, and dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure and the obtained residue was purified by silica gel column chromatography to obtain 1.25 g of N-(1-benzyl-4-methylpiperidin-4-yl)-8-(cyclohexylmethoxy)-2-methylimidazolo[1,2-a]pyridine-3-carboxamide.

Example 34

A mixture of 1.15 g of N-(1-benzyl-4-methylpiperidin-4-yl)-8-(cyclohexylmethoxy)-2- methylimidazolo[1,2-a]pyridine-3-carboxamide, 0.4 mL of 1-chloroethyl chloroformate, and 15 mL of dichloroethane was heated to reflux overnight. After leaving to be cooled at room temperature, the solvent was evaporated under reduced pressure, and to the residue was added 15 mL of methanol, followed by heating to reflux for 6 hours. After leaving to be cooled at room temperature, the solvent was evaporated under reduced pressure, and to the residue were added a saturated aqueous sodium hydrogen carbonate solution and chloroform to carry out a layer separation operation. The organic layer was dried over anhydrous magnesium sulfate and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography to obtain 426 mg of 8-(cyclohexylmethoxy)-2-methyl-N-(4-methylpiperidin-4-yl)imidazolo[1,2-a]pyridine-3-carboxamide.

Example 35

To a solution of 100 mg of (3S)-3-({[8-(cyclohexylmethoxy)-2-methylimidazolo[1,2-a]pyridin-3-yl]carbonyl}amino)-3-phenylpropanoic acid in 1 mL of DMF was added 43 mg of 1,1'-carbonyldiimidazole, followed by stirring for 30 minutes. To the reaction solution were added 24 mg of methanesulfonamide and 0.039 mL of 1,8-diazabicyclo[5.4.0]-7-undecene, followed by stirring for 5 hours. To the reaction mixture were added 1 M hydrochloric acid and ethyl acetate to carry out a layer separation operation. The obtained organic layer was washed with water and saturated brine, and dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure and the residue was purified by silica gel column chromatography. To the purified product were added ethyl acetate and hexane, and the resulting solid was collected by filtration and dried to obtain 41 mg of 8-(cyclohexylmethoxy)-2-methyl-N-{(1S)-3-[(methylsulfonyl)amino]-3-oxo-1-phenylpropyl}imidazolo[1,2-a]pyridine-3-carboxamide.

Example 661

To a suspension of 149 mg of methyl (1S,2R)-1-({[8-(cyclohexylmethoxy)-2-methylimidazo[1,2-a]pyridin-3-yl]carbonyl}amino)-5-methylindane-2-carboxylate in 6 ml of dioxane was added 6 ml of 3 M hydrochloric acid, followed by stirring at 80° C. for 4 hours. After leaving to be cooled, the solvent was evaporated under reduced pressure, and then to the obtained residue were added a saturated aqueous sodium hydrogen carbonate solution, an aqueous citric acid solution, and chloroform to carry out a layer separation operation. The organic layer was dried over anhydrous magnesium sulfate and the solvent was evaporated under reduced pressure. To the obtained residue was added diisopropyl ether, and the insoluble material was collected by filtration and dried to obtain 126 mg of (1S,2R)-1-({[8-(cyclohexylmethoxy)-2-methylimidazo[1,2-a]pyridin-3-yl]carbonyl}amino)-5-methylindane-2-carboxylic acid.

Example 663

4.5 mg of sodium was added to and dissolved in 6 ml of methanol. To the reaction mixture was added 300 mg of methyl rac-(1R,2R)-1-({[8-(cyclohexylmethoxy)-2-methylimidazo[1,2-a]pyridin-3-yl]carbonyl}amino)-1,2,3,4-tetrahydronaphthalene-2-carboxylate, followed by stirring at 90° C. for 5 hours. After leaving to be cooled, the solvent was evaporated under reduced pressure, and then to the obtained residue were added a 10% aqueous citric acid solution and ethyl acetate to carry out a layer separation operation. The organic layer was washed with saturated brine and dried over anhydrous magnesium sulfate, and the solvent was evaporated under reduced pressure. The obtained residue was purified by silica gel column chromatography and washed with ethyl acetate-hexane to obtain 139 mg of methyl rac-(1R,2S)-1-({[8-(cyclohexylmethoxy)-2-methylimidazo[1,2-a]pyridin-3-yl]carbonyl}amino)-1,2,3,4-tetrahydronaphthalene-2-carboxylate.

Example 669

Methyl (1S,2R)-1-({[8-(cyclohexylmethoxy)-2-methylimidazo[1,2-a]pyridin-3-yl]carbonyl}amino)-4-methylindane-2-carboxylate was prepared using the compound of Preparation Example 123 by the same method as in Example 1 as described above.

Example 673

Methyl (1S,2R)-1-[({8-[(2,6-difluorobenzyl)oxy]-2-methylimidazo[1,2-a]pyridin-3-yl}carbonyl)amino]-4-methylindane-2-carboxylate was prepared using the compound of Preparation Example 123 by the same method as in Example 1 as described above.

Example 674

Methyl (1S,2R)-1-[({8-[(2,6-difluorobenzyl)oxy]-2-methylimidazo[1,2-a]pyridin-3-yl}carbonyl)amino]-7-fluoroindane-2-carboxylate was prepared using the compound of Preparation Example 115 by the same method as in Example 1 as described above.

Example 683

Methyl rac-(1R,2R)-1-({[8-(cyclohexylmethoxy)-2-methylimidazo[1,2-a]pyridin-3-yl]carbonyl}amino)-7-fluoroindane-2-carboxylate as a racemate of cis isomers was prepared using the compound of Preparation Example 139 by the same method as in Example 1 as described above.

Example 684

Methyl (1S,2R)-1-({[8-(cyclohexylmethoxy)-2-methylimidazo[1,2-a]pyridin-3-yl]carbonyl}amino)-7-fluoroindane-2-carboxylate was prepared using the compound of Preparation Example 115 by the same method as in Example 1 as described above.

Example 685

Methyl (1R,2S)-1-({[8-(cyclohexylmethoxy)-2-methylimidazo[1,2-a]pyridin-3-yl]carbonyl}amino)-7-fluoroindane-2-carboxylate was prepared using the compound of Preparation Example 140 by the same method as in Example 1 as described above. Further, the compound of Example 684 and the present compound of Example 685 are enantiomers (mirror image isomers) with respect to each other.

Example 693

Preparation was carried out by the same method as in Example 661 as described above using the compound of Example 669.

Example 695

Preparation was carried out by the same method as in Example 661 as described above using the compound of Example 663.

Example 698

Preparation was carried out by the same method as in Example 661 as described above using the compound of Example 673.

Example 699

Preparation was carried out by the same method as in Example 661 as described above using the compound of Example 674.

Example 702

Preparation was carried out by the same method as in Example 661 as described above using the compound of Example 678.

Example 703

Preparation was carried out by the same method as in Example 661 as described above using the compound of Example 683.

Example 704

Preparation was carried out by the same method as in Example 661 as described above using the compound of Example 684.

Example 705

Preparation was carried out by the same method as in Example 661 as described above using the compound of Example 685.

Example 709

To 301 mg of 8-[(2,6-difluorobenzyl)oxy]-N-[2,2-dimethyl-5-(3-methylphenyl)-1,3-dioxan-5-yl]-2-methylimidazo[1,2-a]pyridine-3-carboxamide were added 3 ml of dioxane, 3 ml of methanol, and 6 ml of 1 M hydrochloric acid, followed by stirring for 14 hours. To the reaction mixture were added a saturated aqueous sodium hydrogen carbonate solution, water, and ethyl acetate under ice-cooling to carry out a layer separation operation. The organic layer was washed with a saturated aqueous sodium hydrogen carbonate solution and saturated brine in this order, and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure and the obtained residue was purified by silica gel column chromatography. To the obtained purified product were added hexane and ethyl acetate, and the insoluble material was collected by filtration and dried to obtain 172 mg of 8-[(2,6-difluorobenzyl)oxy]-N-[1,3-dihydroxy-2-(3-methylphenyl)propan-2-yl]-2-methylimidazo[1,2-a]pyridine-3-carboxamide.

Example 710

To 252 mg of diethyl[({8-[(2,6-difluorobenzyl)oxy]-2-methylimidazo[1,2-a]pyridin-3-yl}carbonyl)amino]malonate were added 4 ml of ethanol, 0.23 ml of a 20% sodium ethoxide/ethanol solution, and 0.31 ml of 1-iodobutane, followed by stirring at 70° C. for 3 hours. Subsequently, 11 mg of sodium ethoxide was added thereto, followed by stirring at 70° C. for 1 hour. To the reaction mixture were added an aqueous citric acid solution, a saturated aqueous sodium hydrogen carbonate solution, and chloroform to carry out a layer separation operation. The organic layer was dried over anhydrous sodium sulfate and the solvent was evaporated under reduced pressure. The obtained residue was purified by silica gel column chromatography to obtain 69 mg of diethyl butyl[({8-[(2,6-difluorobenzyl)oxy]-2-methylimidazo[1,2-a]pyridin-3-yl}carbonyl)amino]malonate.

Example 711

To a mixture of 68 mg of diethyl butyl[({8-[(2,6-difluorobenzyl)oxy]-2-methylimidazo[1,2-a]pyridin-3-yl}carbonyl)amino]malonate in 1.4 ml of ethanol was added a solution of 35 mg of calcium chloride in 0.34 ml of water. Subsequently, 24 mg of sodium borohydride was added thereto under ice-cooling, followed by stirring for 1 hour under ice-cooling and at room temperature for 4 hours. Further, 2 ml of ethanol, a solution of 35 mg of calcium chloride in 0.34 ml of water, and 24 mg of sodium borohydride were added thereto followed by stirring at room temperature for 15 hours. Further, a solution of 35 mg of calcium chloride in 0.34 ml of water and 24 mg of sodium borohydride were added thereto, followed by stirring at room temperature for 15 hours. To the reaction mixture were added 1 M hydrochloric acid and ethyl acetate to carry out a layer separation operation. The organic layer was washed with saturated brine and dried over anhydrous sodium sulfate, and the solvent was evaporated under reduced pressure. The obtained residue was purified by silica gel column chromatography to obtain 32 mg of 8-[(2,6-difluorobenzyl)oxy]-N-[1-hydroxy-2-(hydroxymethyl)hexan-2-yl]-2-methylimidazo[1,2-a]pyridine-3-carboxamide.

Example 712

To a solution of 229 mg of methyl rac-(1R,2R)-1-[({8-[(2,6-difluorobenzyl)oxy]-2-methylimidazo[1,2-a]pyridin-3-yl}carbonyl)amino]-2-hydroxyindane-1-carboxylate in 3.4 ml of ethanol and 0.68 ml of THF was added 68 mg of sodium borohydride under ice-cooling, followed by stirring at room temperature for 4 hours. To the reaction mixture were added 1 M hydrochloric acid and ethyl acetate to carry out a layer separation operation. The organic layer was washed with saturated brine and dried over anhydrous magnesium sulfate, and the solvent was evaporated under reduced pressure. The obtained residue was purified by silica gel column chromatography. To the obtained purified product was added diisopropyl ether, and the resulting solid was collected by filtration and dried to obtain 74 mg of rac-8-[(2,6-difluorobenzyl)oxy]-N-[(1R,2S)-2-hydroxy-1-(hydroxymethyl)-2,3-dihydro-1H-indan-1-yl]-2-methylimidazo[1,2-a]pyridine-3-carboxamide.

Example 713

To 100 mg of 1-({[8-(cyclohexylmethoxy)-2-methylimidazo[1,2-a]pyridin-3-yl]carbonyl}oxy)-1H-benzotriazole were 1.7 ml of dichloromethane, 0.065 ml of (S)-(−)-1-phenylethylamine, and 0.07 ml of triethylamine, followed by stirring overnight. To the reaction mixture were added water and chloroform to carry out a layer separation operation, followed by drying over anhydrous sodium sulfate, and the solvent was evaporated under reduced pressure. The obtained residue was purified by silica gel column chromatography. To the obtained purified product was added diisopropyl ether, and the resulting solid was collected by filtration and dried to obtain 80 mg of 8-(cyclohexylmethoxy)-2-methyl-N-[(1S)-1-phenylethyl]imidazo[1,2-a]pyridine-3-carboxamide.

Example 714

To a mixture of 100 mg of the compound of Example 766 in 3.3 ml of THF and 1.7 ml of water was added 65 mg of sodium periodate under ice-cooling, followed by stirring at room temperature for 2 hours and at 50° C. for 3 hours. To the reaction mixture were added water and ethyl acetate to carry out a layer separation operation. The organic layer was washed with saturated brine and dried over anhydrous sodium sulfate, and the solvent was evaporated under reduced pressure. To a mixture of the obtained residue in 2 ml of THF and 2 ml of methanol was added 39 mg of sodium borohydride under ice-cooling, followed by stirring for 1 hour under ice-cooling and at room temperature for 1 hour. To the reaction mixture were added a saturated aqueous ammonium chloride solution, ethyl acetate, and water to carry out a layer separation operation. The organic layer was washed with saturated brine and dried over anhydrous magnesium sulfate, the solvent was evaporated under reduced pressure, and the obtained residue was purified by silica gel column chromatography. The obtained purified product was washed with ethyl acetate and hexane to obtain 33 mg of 8-[(2,6-difluorobenzyl)oxy]-N-(1,5-dihydroxy-3-phenylpentan-3-yl)-2-methylimidazo[1,2-a]pyridine-3-carboxamide.

Example 758

Preparation was carried out using the compound of Preparation Example 240 by the same method as in Example 1 as described above.

Example 759

Preparation was carried out using the compound of Preparation Example 172 by the same method as in Example 1 as described above.

Example 766

Preparation was carried out using the compound of Preparation Example 278 by the same method as in Example 1 as described above.

Example 767

Preparation was carried out using the compound of Preparation Example 279 by the same method as in Example 1 as described above.

Example 797

Preparation was carried out using the compound of Preparation Example 172 by the same method as in Example 1 as described above.

Example 798

Preparation was carried out using the compound of Preparation Example 172 by the same method as in Example 1 as described above.

TABLE 2

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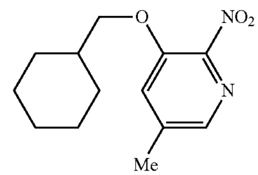
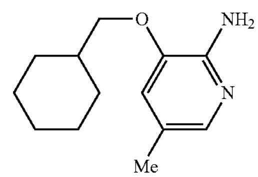
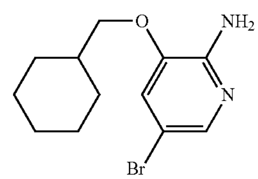
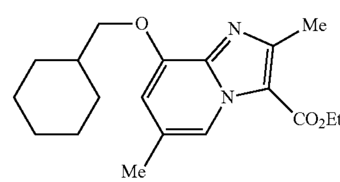
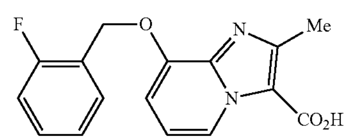
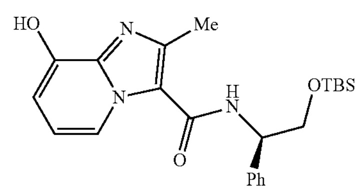
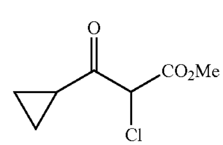
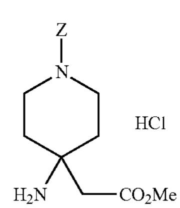
1	
2	
3	
4	
5	
6	
7	
8	

TABLE 2-continued

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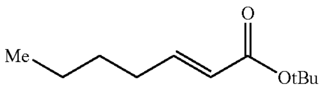
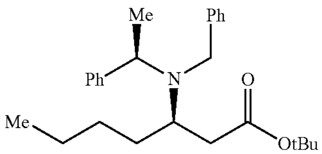
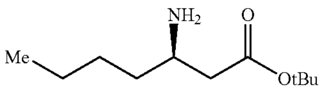
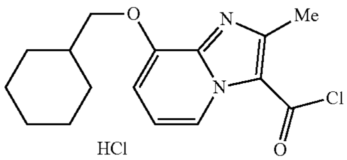
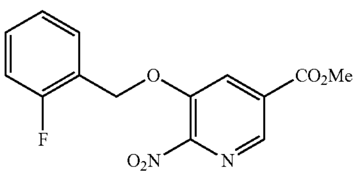
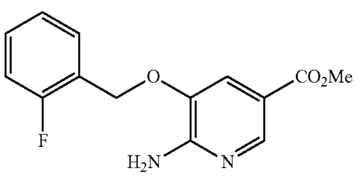
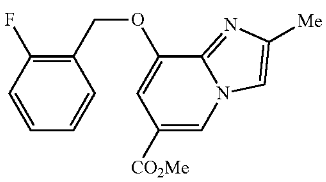
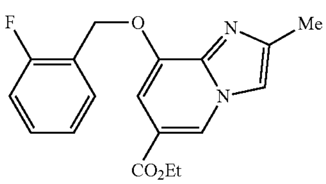
9	
10	
11	
12	
13	
14	
15	
16	

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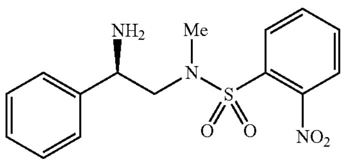
17	

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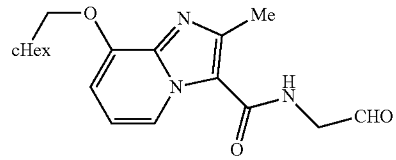
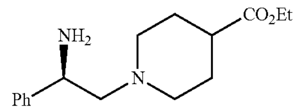
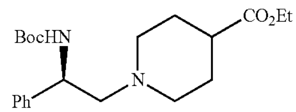
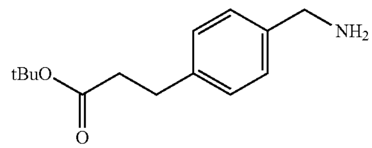
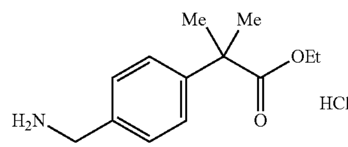
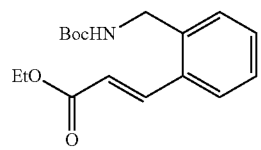
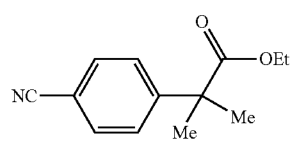
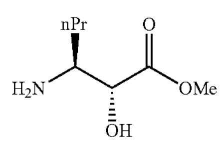
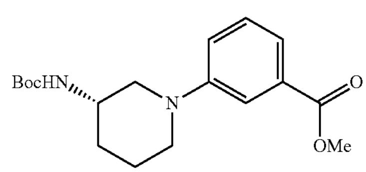
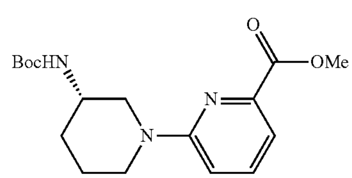
18	
19	
20	
21	
22	
23	
24	
25	
26	
27	

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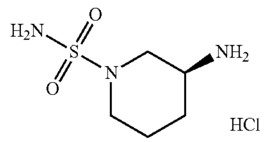
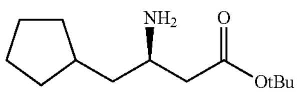
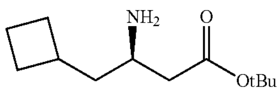
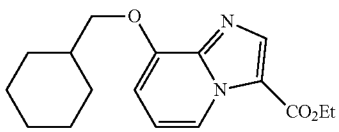
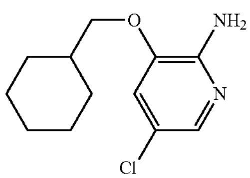
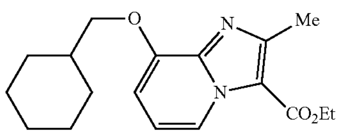
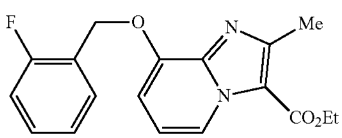
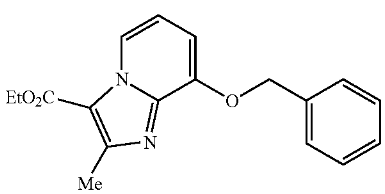
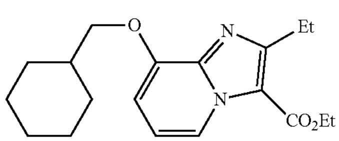
28	
29	
30	
31	
32	
33	
34	
35	
36	

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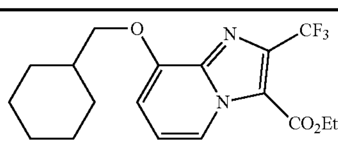
37	

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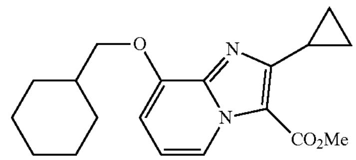
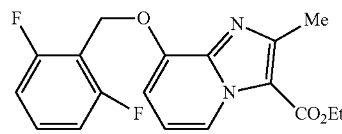
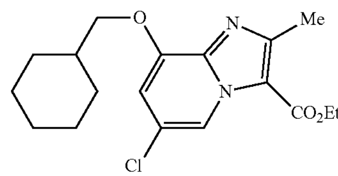
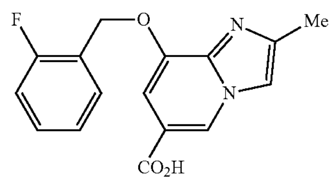
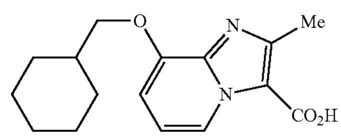
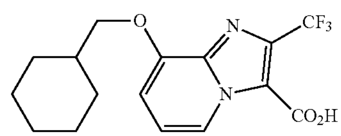
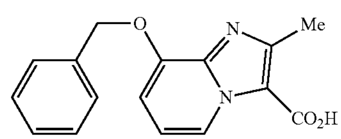
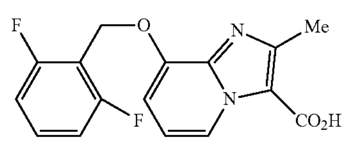
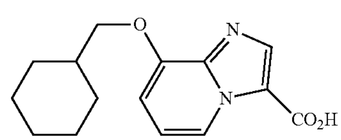
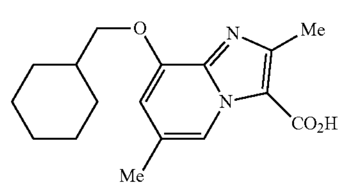
38	
39	
40	
41	
42	
43	
44	
45	
46	
47	

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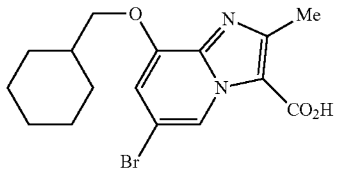
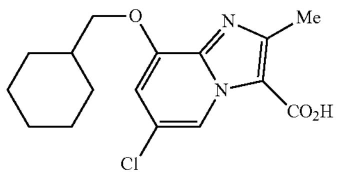
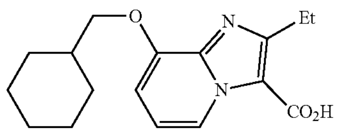
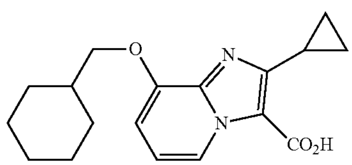
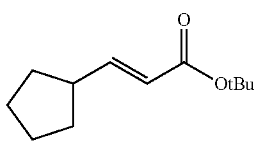
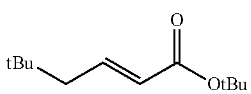
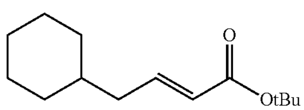
48	
49	
50	
51	
52	
53	
54	

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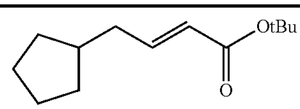
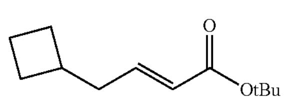
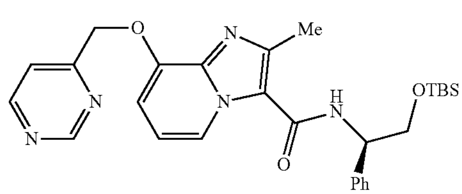
55	
56	
57	

TABLE 5-continued

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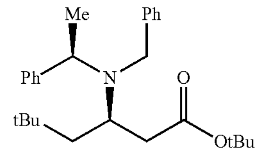
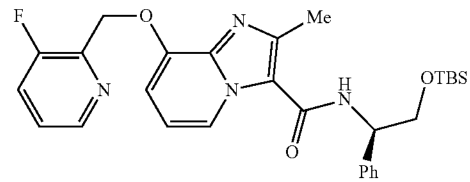
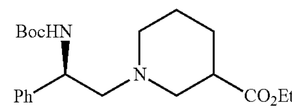
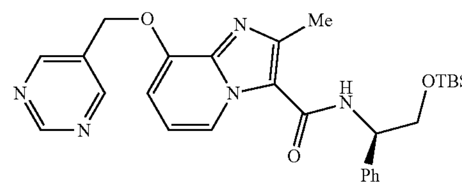
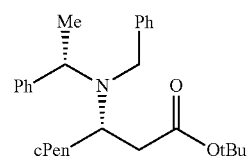
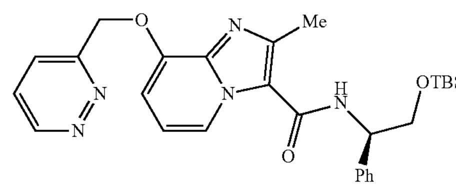
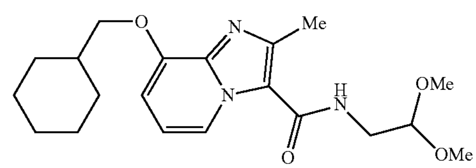
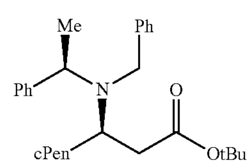
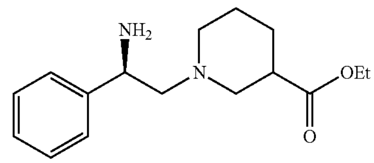
58	
59	
60	
61	
62	
63	
64	
65	
66	

TABLE 5-continued

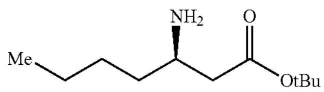
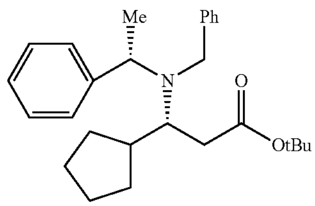
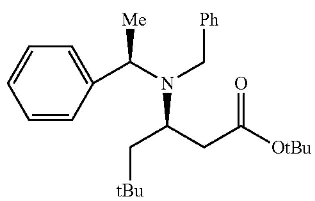
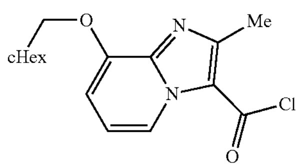
PEx	Str
67	
68	
69	
70	 HCl

TABLE 6

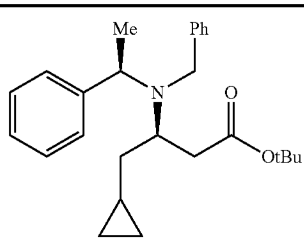
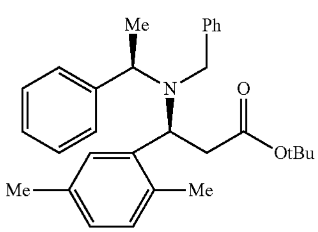
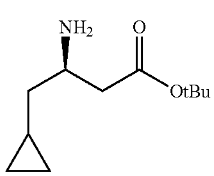
PEx	Str
71	
72	
73	

TABLE 6-continued

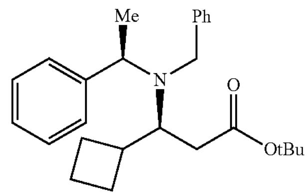
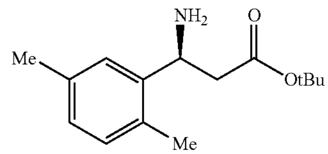
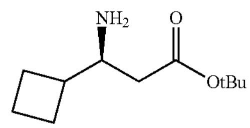
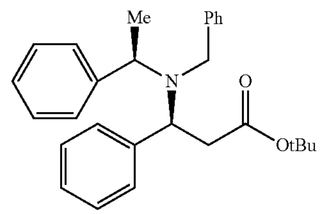
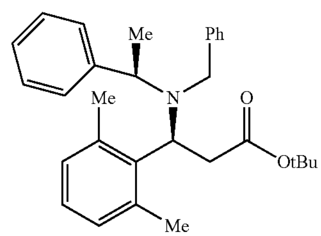
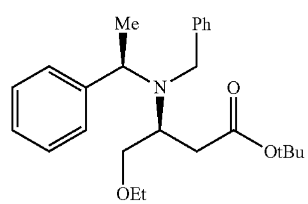
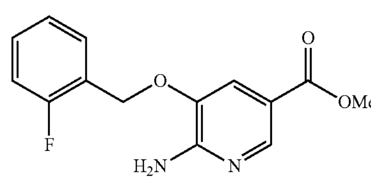
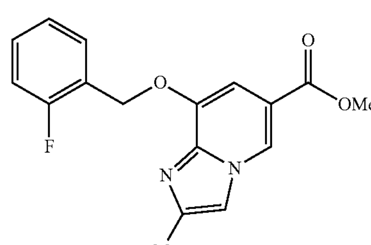
PEx	Str
74	
75	
76	
77	
78	
79	
80	
81	

TABLE 6-continued

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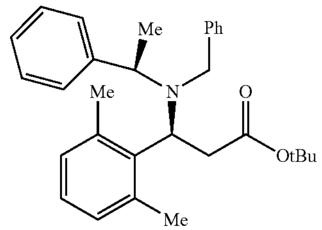
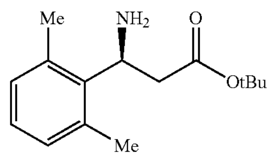
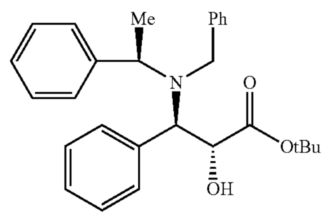
82	
83	
84	

TABLE 7

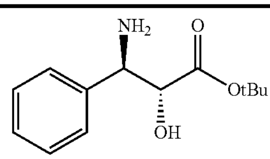
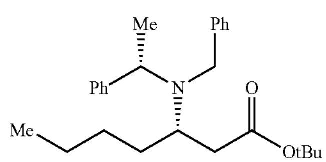
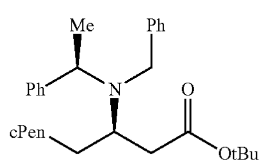
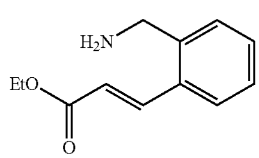
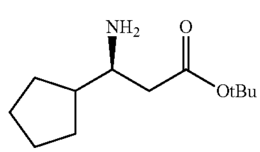
PEx	Str
85	
86	
87	
88	 HCl
89	

TABLE 7-continued

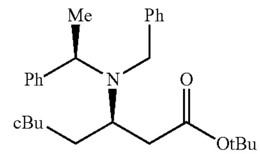
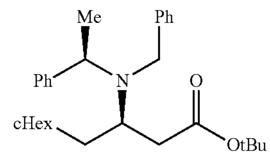
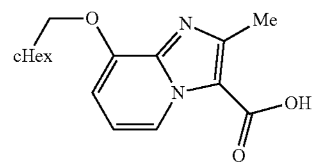
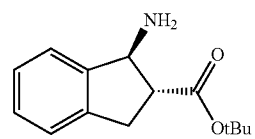
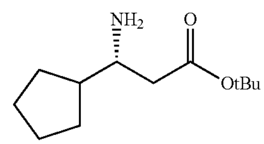
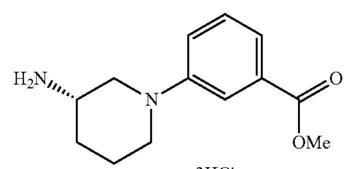
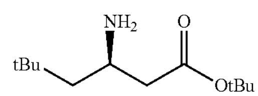
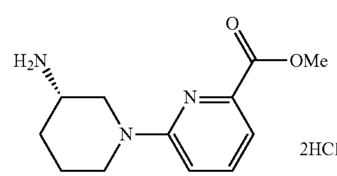
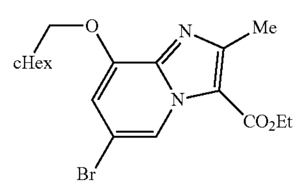
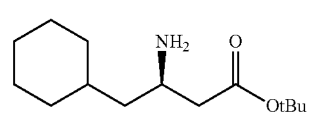
PEx	Str
90	
91	
92	
93	
94	
95	 2HCl
96	
97	 2HCl
98	
99	

TABLE 8

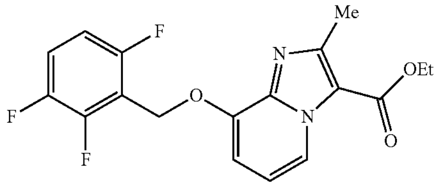
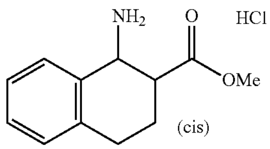
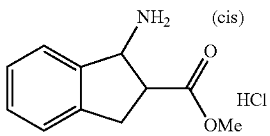
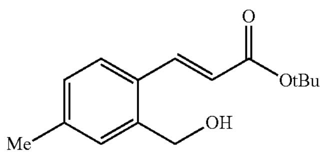
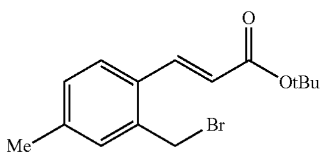
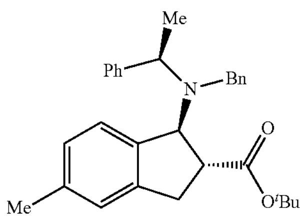
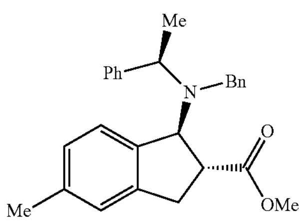
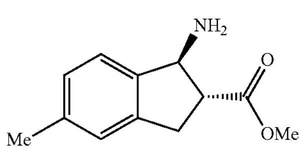
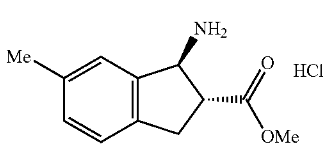
PEx	Str
100	
101	
102	
104	
105	
106	
107	
108	
109	

TABLE 8-continued

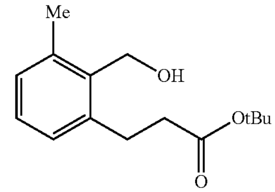
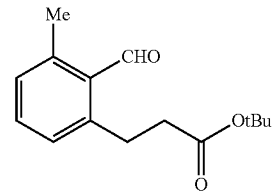
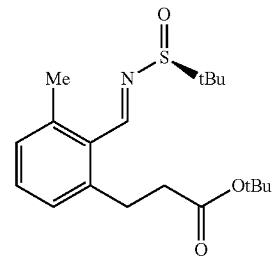
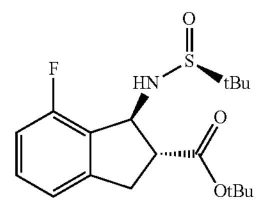
PEx	Str
110	
111	
112	
113a	

TABLE 9

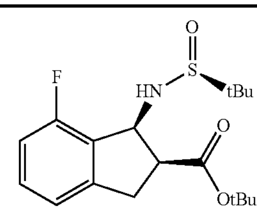
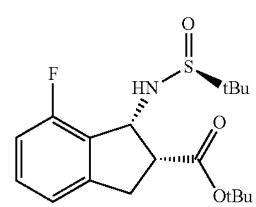
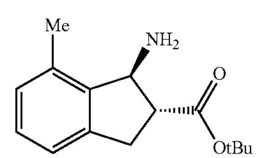
PEx	Str
113b	 or
113c	
114	

TABLE 9-continued

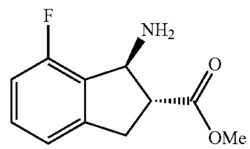
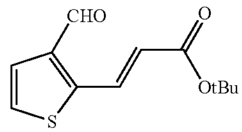
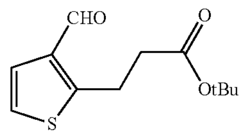
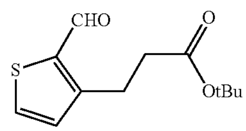
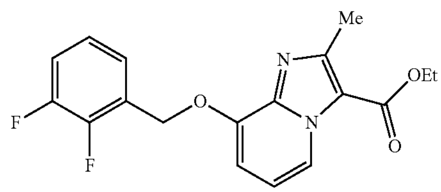
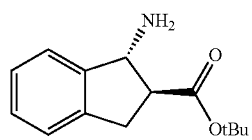
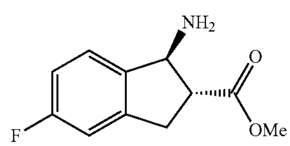
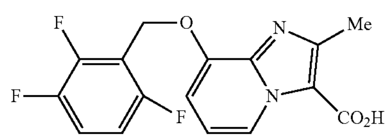
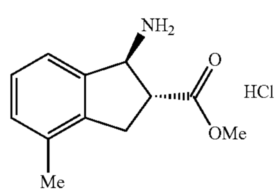
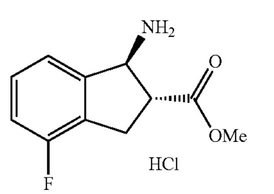
PEx	Str
115	
116	
117	
118	
119	
120	
121	
122	
123	
124	

TABLE 9-continued

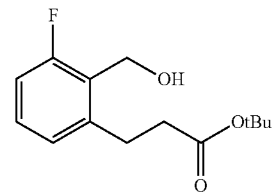
PEx	Str
125	

TABLE 10

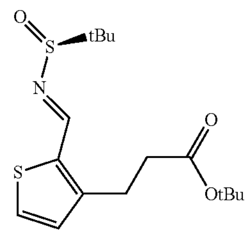
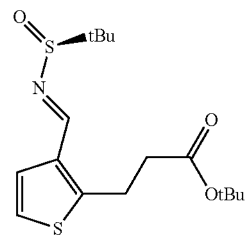
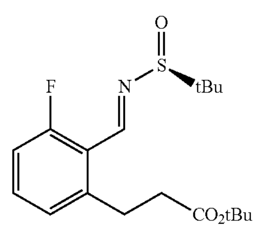
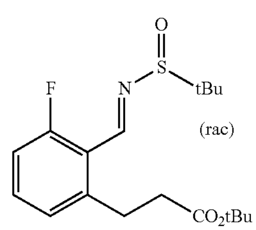
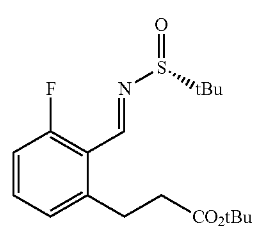
PEx	Str
127	
128	
129	
130	
131	

TABLE 10-continued

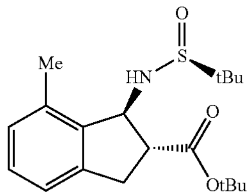
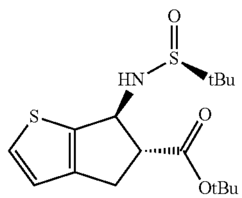
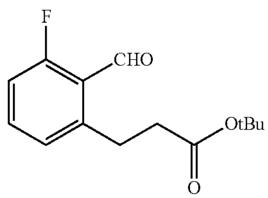
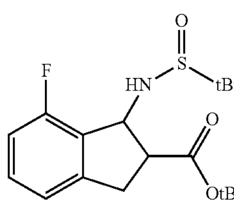
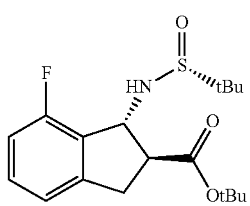
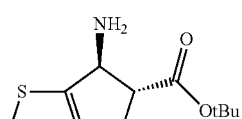
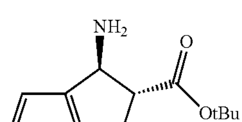
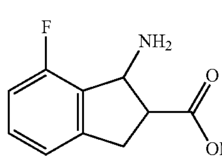
PEx	Str
132	
133	
134	
135	 (cis)
136	
137	 HCl
138	 HCl
139	 (cis)

TABLE 10-continued

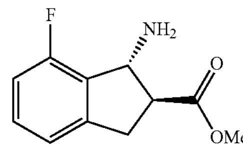
PEx	Str
140	

TABLE 11

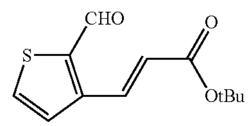
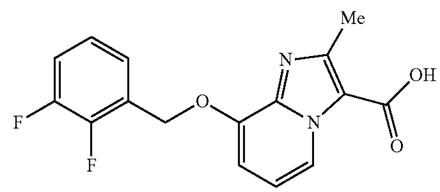
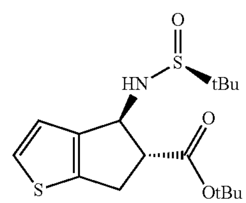
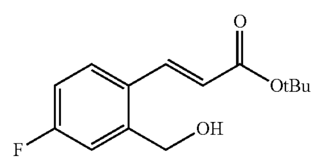
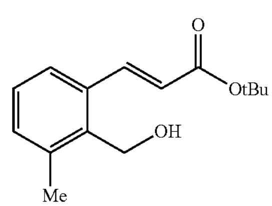
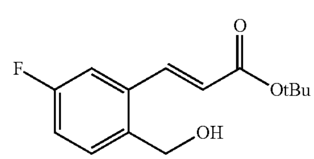
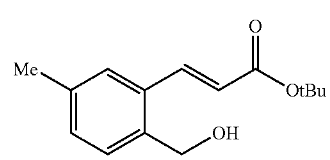
PEx	Str
141	
142	
143	
144	
145	
146	
147	

TABLE 11-continued

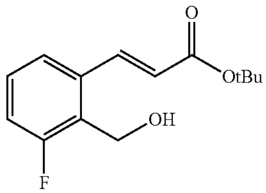
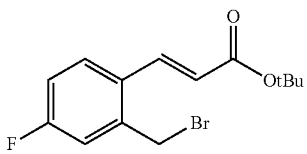
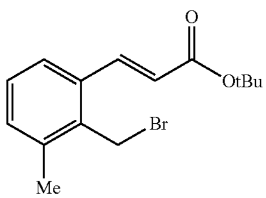
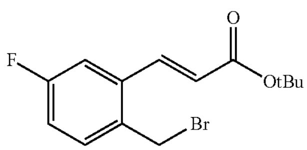
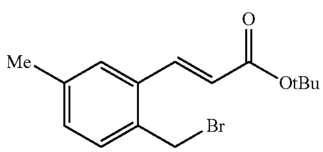
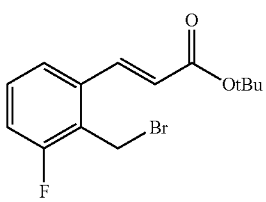
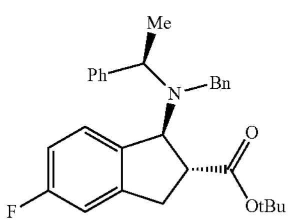
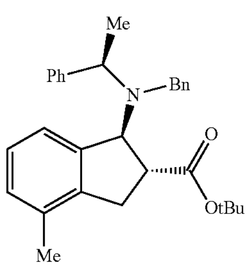
PEx	Str
148	
149	
150	
151	
152	
153	
154	
155	

TABLE 11-continued

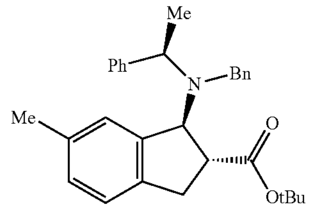
PEx	Str
156	

TABLE 12

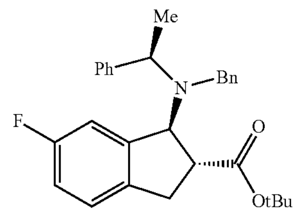
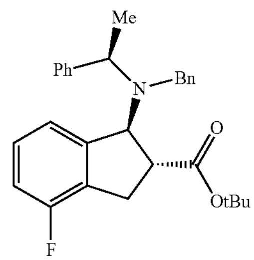
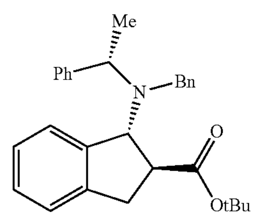
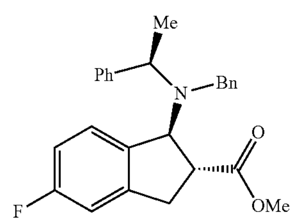
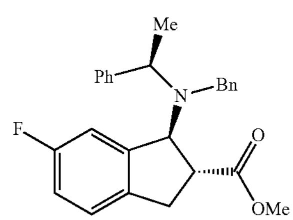
PEx	Str
157	
158	
159	
160	
161	

TABLE 12-continued

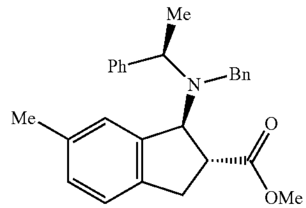
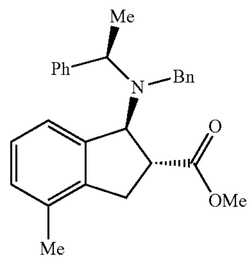
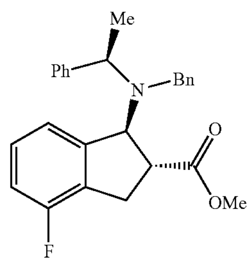
PEx	Str
162	
163	
164	

TABLE 13

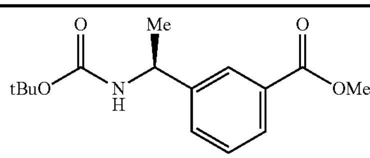
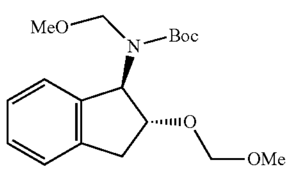
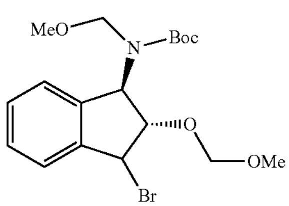
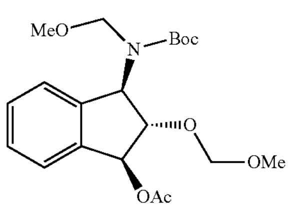
PEx	Str
165	
166	
167	
168a	

TABLE 13-continued

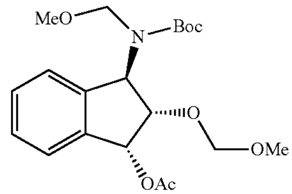
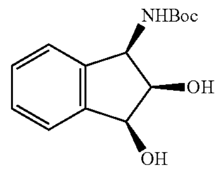
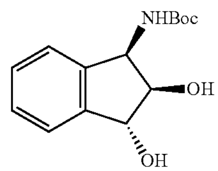
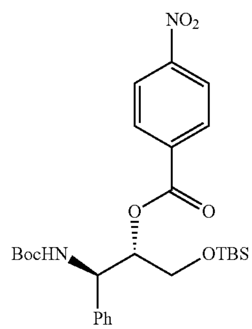
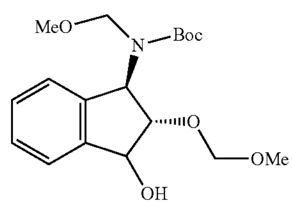
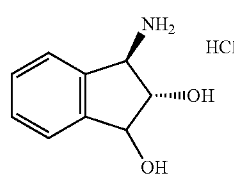
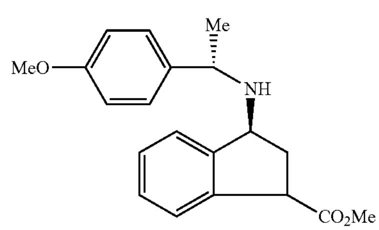
PEx	Str
168b	
169a	
169b	
170	
171	
172	
173	

TABLE 13-continued

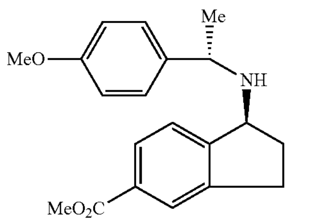
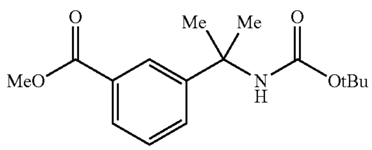
PEx	Str
174	
175	

TABLE 14

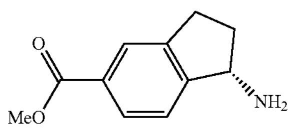
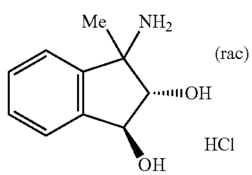
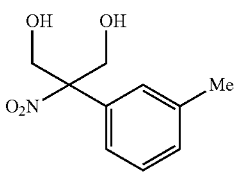
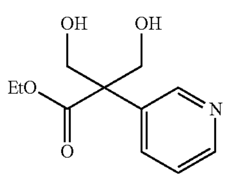
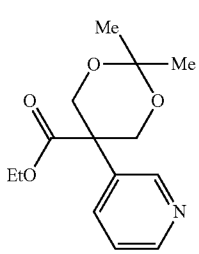
PEx	Str
176	
177	
178	
179	
180	

TABLE 14-continued

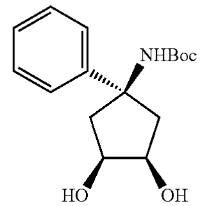
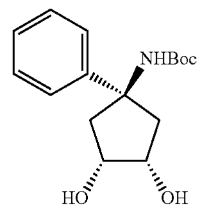
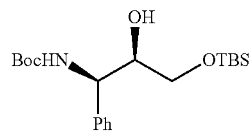
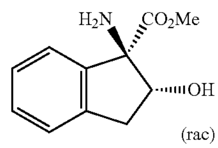
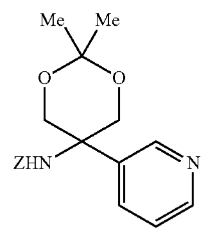
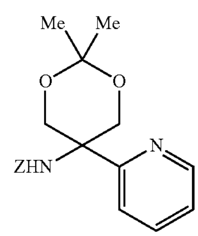
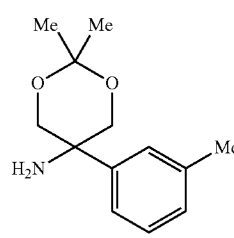
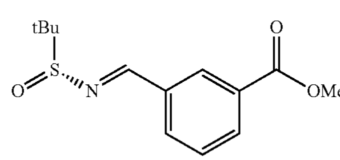
PEx	Str
181a	
181b	
182	
183	
184	
185	
186	
187	

TABLE 14-continued

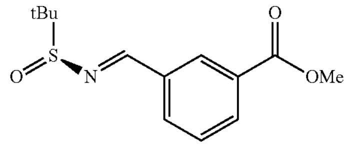
PEx	Str
188	

TABLE 15

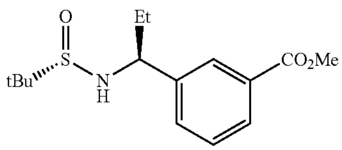
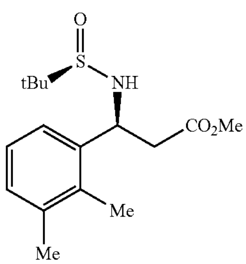
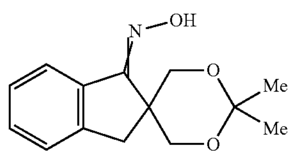
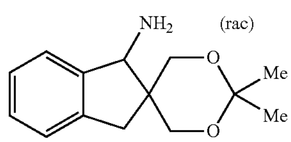
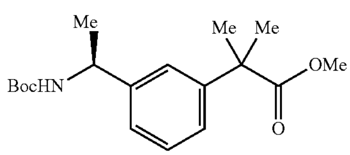
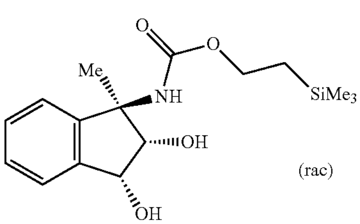
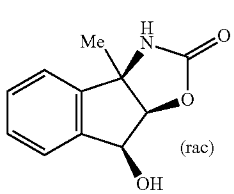
PEx	Str
189	
190	
191	
192	 (rac)
193	
194a	 (rac)
194b	 (rac)

TABLE 15-continued

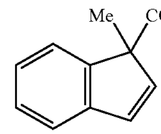
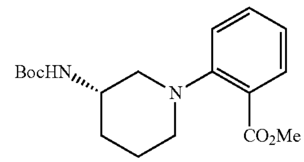
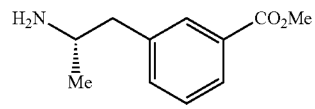
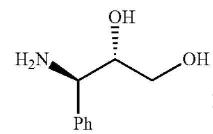
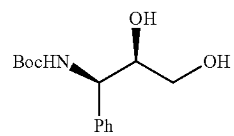
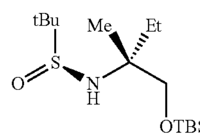
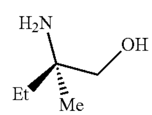
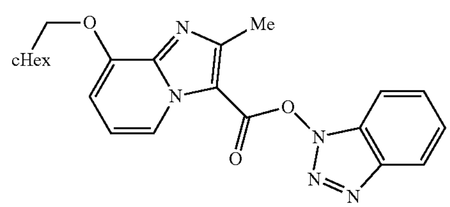
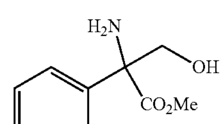
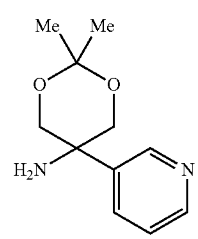
PEx	Str
195	 (rac)
196	
197	
198	 HCl
199	
200	
201	 HCl
202	
203	 (rac)
204	

TABLE 16

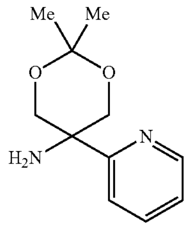
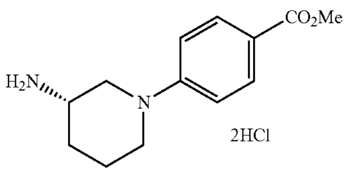
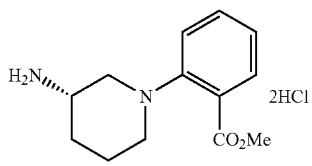
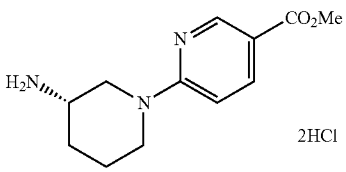
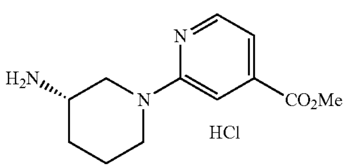
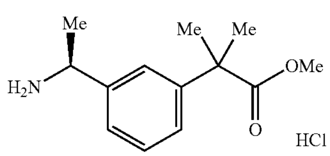
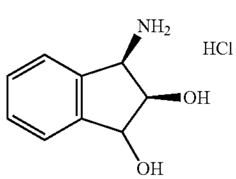
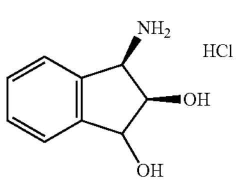
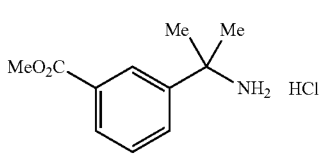
PEx	Str
205	
206	
207	
208	
209	
210	
211	
212	
213	

TABLE 16-continued

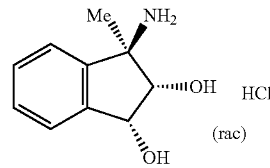
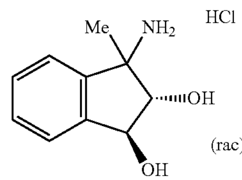
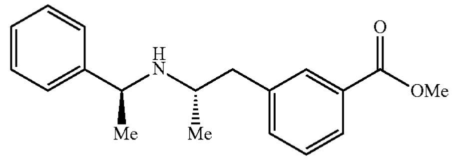
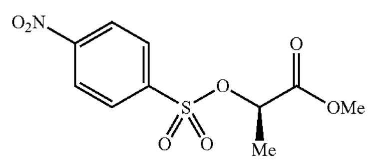
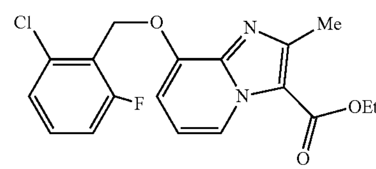
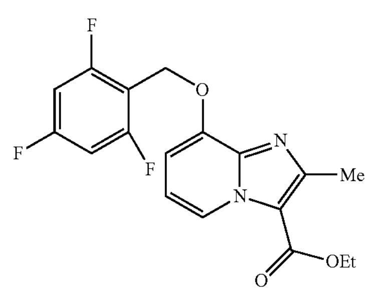
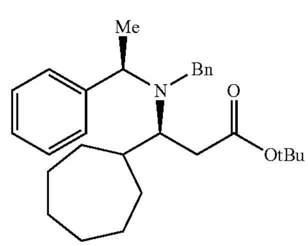
PEx	Str
214	
215	
216	
217	
218	
219	
230	

TABLE 17

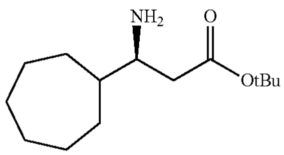
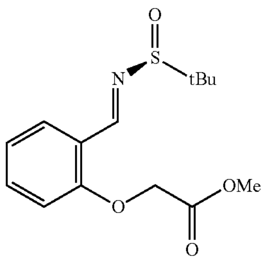
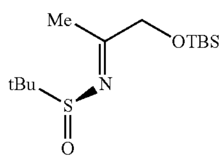
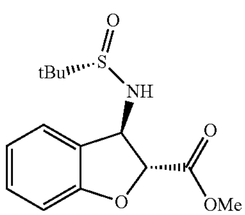
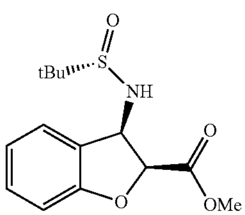
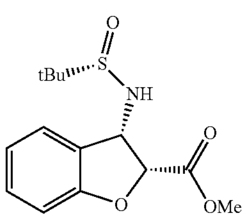
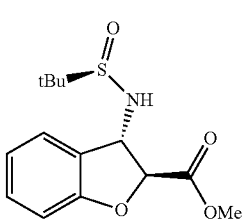
PEx	Str
221	
222	
223	
224a	
224b	 or 
225a	

TABLE 17-continued

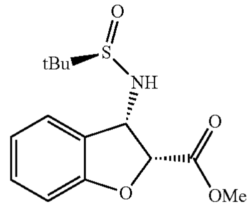
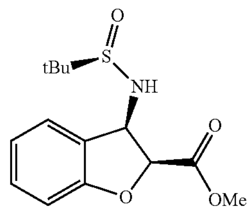
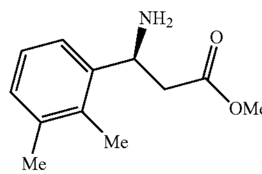
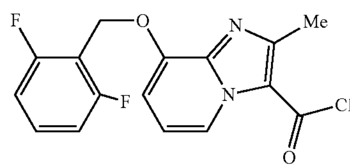
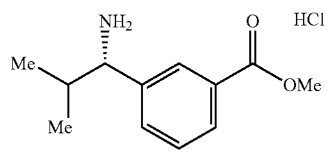
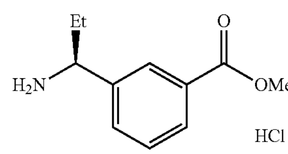
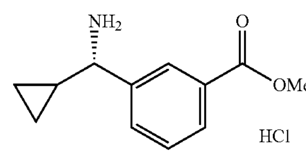
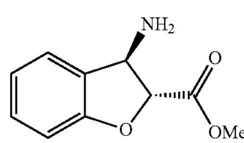
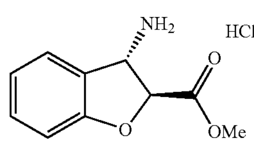
PEx	Str
225b	 or 
226	
227	 HCl
228	 HCl
229	 HCl
230	 HCl
231	 HCl
232	 HCl

TABLE 18

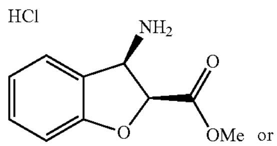
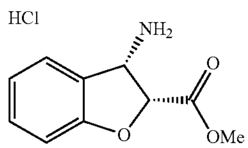
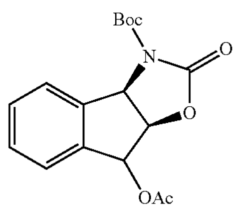
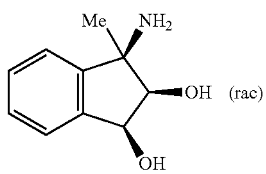
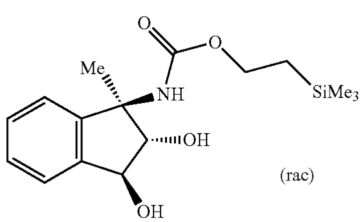
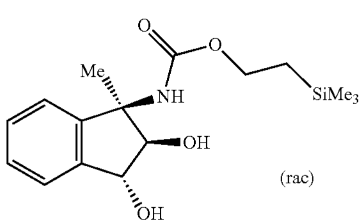
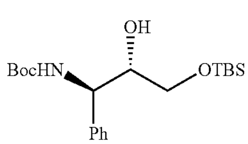
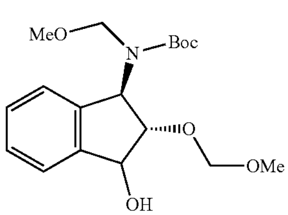
PEx	Str
233	
234	
235	
236	
237a	
237b	
238	
239	

TABLE 18-continued

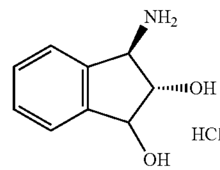
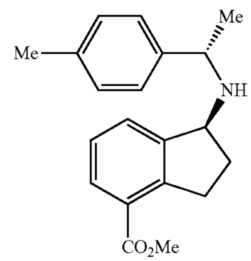
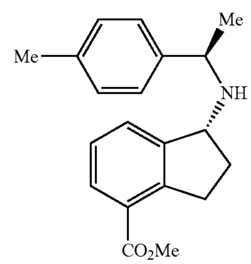
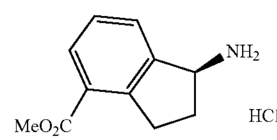
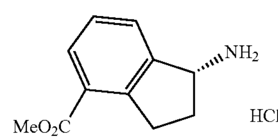
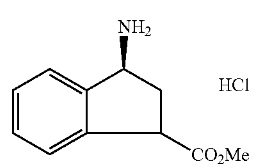
PEx	Str
240	
241	
242	
243	
244	
245	

TABLE 19

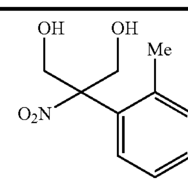
PEx	Str
246	

TABLE 19-continued

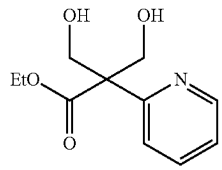
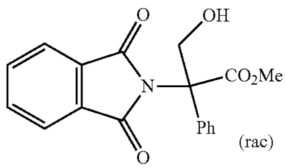
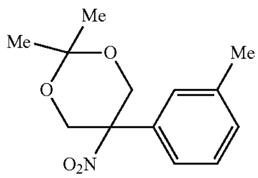
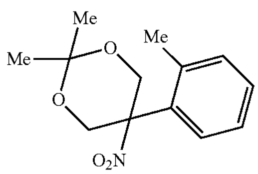
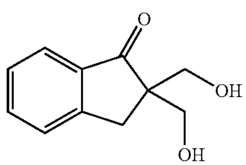
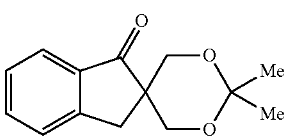
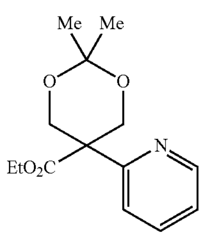
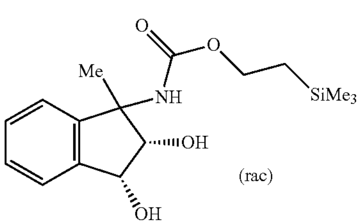
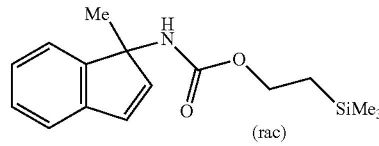
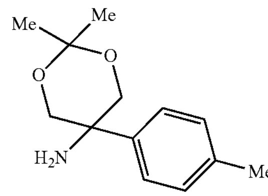
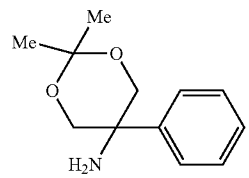
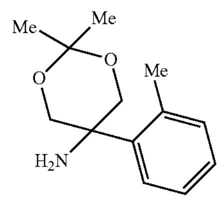
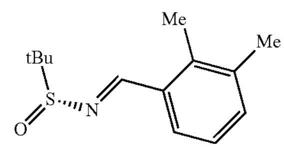
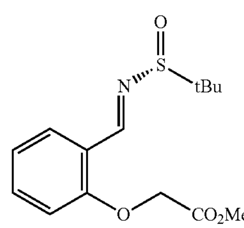
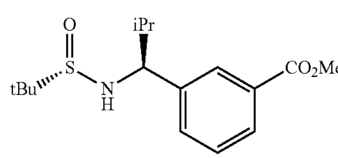
PEx	Str
247	
248	
249	
250	
251	
252	
253	
254	
255	
256	
257	
258	
259	
260	
261	

TABLE 20

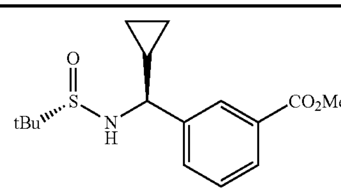
PEx	Str
262	

TABLE 20-continued

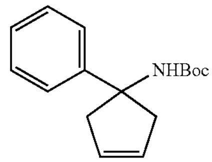
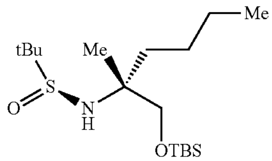
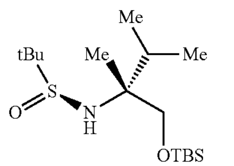
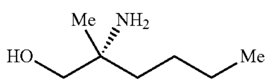
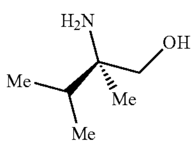
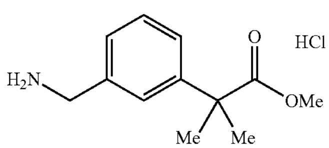
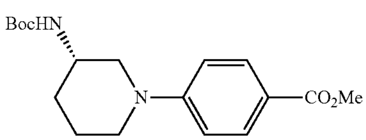
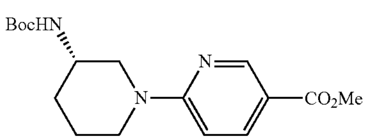
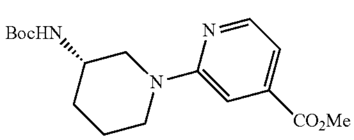
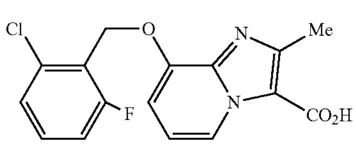
PEx	Str
263	
264	
265	
266	
267	
268	
269	
270	
271	
272	

TABLE 20-continued

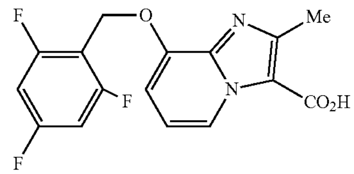
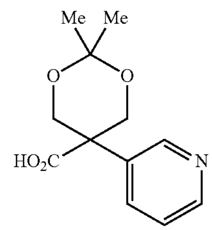
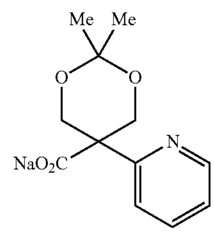
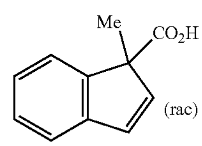
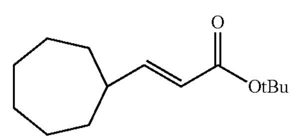
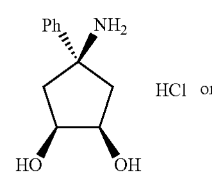
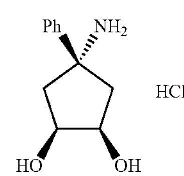
PEx	Str
273	
274	
275	
276	
277	
278	
279	

TABLE 21

PEx	Syn	Dat
1	PEx1	ESI+: 251
2	PEx2	ESI+: 221
3	PEx3	ESI+: 285
4	PEx4	ESI+: 331
5	PEx5	ESI+: 301
6	PEx6	ESI+: 426
7	PEx7	CI+: 177, 179
8	PEx8	ESI+: 307

TABLE 21-continued

PEx	Syn	Dat
9	PEx9	ESI+: 185
10	PEx10	ESI+: 396
11	PEx11	ESI+: 202
12	PEx12	NMR(DMSO-d_6): 1.07-1.36 (5H, m), 1.63-1.80 (2H, m), 1.82-1.96 (2H, m), 2.76 (3H, s), 4.13 (2H, d, J = 6 Hz), 7.52-7.47 (1H, m), 7.58 (1H, d, J = 8 Hz), 9.08 (1H, d, J = 6 Hz)
13	PEx13	FAB+: 307
14	PEx14	EI: 276
15	PEx15	EI: 314
16	PEx16	ESI+: 329
17	PEx17	ESI+: 336
18	PEx18	ESI+: 330
19	PEx19	ESI+: 277
20	PEx20	ESI+: 377
21	PEx21	NMR($CDCl_3$): 1.42 (9H, s), 2.52 (2H, t, J = 8 Hz), 2.89 (2H, t, J = 8 Hz), 3.84 (2H, s), 7.17 (2H, d, J = 8 Hz), 7.23 (2H, d, J = 8 Hz)
22	PEx22	NMR(DMSO-d_6): 1.12 (3H, t, J = 8 Hz), 1.49 (6H, s), 3.98 (2H, s), 4.06 (2H, q, J = 7 Hz), 7.34 (2H, d, J = 8 Hz), 7.46 (2H, d, J = 8 Hz), 8.44 (3H, br s)
23	PEx23	NMR($CDCl_3$): 1.34 (3H, t, J = 7 Hz), 1.46 (9H, s), 4.27 (2H, q, J = 7 Hz), 4.46 (2H, d, J = 5 Hz), 4.73 (1H, brs), 6.37 (1H, d, J = 16 Hz), 7.28-7.36 (3H, m), 7.57 (1H, d, J = 8 Hz), 7.95 (1H, d, J = 16 Hz)
24	PEx24	NMR($CDCl_3$): 1.18 (3H, t, J = 7 Hz), 1.58 (6H, s), 4.13 (2H, q, J = 7 Hz), 7.45 (2H, dt, J = 9, 2 Hz), 7.62 (2H, dt, J = 9, 2 Hz)

TABLE 22

PEx	Syn	Dat
25	PEx25	ESI+: 162
26	PEx 26	ESI+: 335
27	PEx 27	ESI+: 336
28	PEx28	ESI+: 180
29	PEx11	CI+: 228
30	PEx11	ESI+: 214
31	PEx15	ESI+: 303
32	PEx3	ESI+: 241
33	PEx4	ESI+: 317
34	PEx4	ESI+: 329
35	PEx4	ESI+: 311
36	PEx4	ESI+: 317
37	PEx4	ESI+: 371
38	PEx4	ESI+: 329
39	PEx4	ESI+: 347
40	PEx4	ESI+: 351
41	PEx5	ESI+: 301
42	PEx5	ESI+: 289
43	PEx5	ESI+: 343
44	PEx5	ESI+: 283
45	PEx5	ESI+: 319
46	PEx5	ESI+: 275
47	PEx5	ESI+: 303
48	PEx5	ESI+: 367
49	PEx5	ESI+: 323, 325
50	PEx5	ESI+: 303
51	PEx5	ESI+: 315
52	PEx9	ESI+: 197
53	PEx9	CI+: 199
54	PEx9	CI+: 225
55	PEx9	EI: 210
56	PEx9	ESI+: 197
57	Ex2	ESI+: 518
58	PEx10	ESI+: 410

TABLE 23

PEx	Syn	Dat
59	Ex2	ESI+: 535
60	PEx20	ESI+: 377
61	Ex2	ESI+ 518
62	PEx10	ESI+: 408
63	Ex2	ESI+: 518
64	Ex1	ESI+: 376
65	PEx10	ESI+: 408
66	PEx19	ESI+: 277
67	PEx11	ESI+: 202
68	PEx10	ESI+: 408
69	PEx10	ESI+: 410
70	PEx12	NMR(DMSO-d_6): 1.07-1.36 (5H, m), 1.63-1.80 (2H, m), 1.82-1.96 (2H, m), 2.49-2.53 (2H, m), 2.76 (3H, s), 4.13 (2H, d, J = 6 Hz), 7.52-7.47 (1H, m), 7.58 (1H, d, J = 8 Hz), 9.08 (1H, d, J = 6 Hz)
71	PEx9, 10	ESI+: 394
72	PEx9, 10	ESI+: 443
73	PEx 11	ESI+: 200
74	PEx9, 10	ESI+: 394
75	PEx11	ESI+: 250
76	PEx11	ESI+: 200
77	PEx10	ESI+: 416
78	PEx10	ESI+: 444
79	PEx10	ESI+: 370
80	PEx14	EI: 276
81	PEx15	EI: 314
82	PEx10	ESI+: 444
83	PEx11	ESI+: 250
84	PEx10	ESI+: 432
85	PEx11	ESI+: 238
86	PEx10	ESI+: 396
87	PEx10	ESI+: 422
88	Ex5	ESI+: 206
89	PEx11	ESI+: 214
90	PEx10	ESI+: 408

TABLE 24

PEx	Syn	Dat
91	PEx10	ESI+: 436
92	PEx5	ESI+: 289
93	PEx11	ESI+: 234
94	PEx11	ESI+: 214
95	Ex5	ESI+: 235
96	PEx11	ESI+: 216
97	Ex5	ESI+: 236
98	PEx4	ESI+: 395
99	PEx11	ESI+: 242

TABLE 25

PEx	Syn	Dat
100	PEx1	ESI+: 365
101	PEx101	APCI/ESI+: 206
102	PEx 102	ESI+: 192
104	PEx104	ESI+: 249
105	PEx105	ESI+: 311, 313
106	PEx106	ESI+: 442
107	PEx107	ESI+: 400
108	PEx11	ESI+: 206
109	PEx109	ESI+: 206
110	PEx110	ESI+: 273 [M + Na]+
111	PEx111	ESI+: 249
112	PEx112	ESI+: 352
113a	PEx113	ESI+: 356
		NMR($CDCl_3$): 1.21 (9H, s), 1.48 (9H, s), 3.15 (1 H, dd, J = 6.6, 16.4 Hz), 3.40 (1H, dd, J = 9.0, 16.4 Hz), 3.50 (1H, ddd, J = 5.4, 6.6, 9.0 Hz), 3.98 (1H, d, J = 3.4 Hz), 5.38 (1H, dd, J = 3.4, 5.0 Hz), 6.89 (1H, dt, Jd = 0.5 Hz, Jt = 9.0 Hz), 7.02 (1H, d, J = 7.5 Hz), 7.23-7.28 (1H, m)

TABLE 25-continued

PEx	Syn	Dat
113b	PEx113	ESI+: 356 NMR($CDCl_3$): 1.15 (9H, s), 1.52 (9H, s), 3.08 (1 H, dd, J = 8.2, 16.1 Hz), 3.33 (1H, ddd, J = 6.8, 8.2, 10.2 Hz), 3.59 (1H, dd, J = 10.2, 16.1 Hz), 4.38 (1H, d, J = 3.9 Hz), 5.18 (1H, dd, J = 3.9, 6.8 Hz), 6.90 (1H, t, J = 8.6 Hz), 7.05 (1H, d, J = 7.6 Hz), 7.25-7.30 (1H, m)
113c	PEx113	ESI+: 356 NMR($CDCl_3$): 1.14 (9H, s), 1.51 (9H, s), 3.10 (1 H, dd, J = 8.1, 16.1 Hz), 3.27 (1H, dd, J = 8.0, 16.0 Hz), 3,42 (1H, dt, Jd = 6,3 Hz, Jt = 8.1 Hz), 4.50 (1H, d, J = 6.0 Hz), 5.22 (1H, t, J = 6.2 Hz), 6.91 (1H, t, J = 8.7 Hz), 7.02 (1H, d, J = 7.4 Hz), 7.22-7.27 (1H, m)
114	PEx114	ESI+: 248
115	PEx115	ESI+: 210
116	PEx116	ESI+: 239
117	PEx117	ESI+: 241
118	Ex15	NMR($CDCl_3$): 1.41 (9H, s), 2.60 (2H, t, J = 7 Hz), 3.26 (2H, t, J = 7 Hz), 7.04 (1H, dd, J = 1, 5 Hz), 7.65 (1H, d, J = 5 Hz), 10.07 (1H, d, J = 1 Hz)
119	PEx1	ESI+: 347
120	PEx11	ESI+: 234
121	PEx11	ESI+: 210
122	PEx5	ESI+: 337
123	PEx109	ESI+: 206
124	PEx109	ESI+: 210
125	PEx110	ESI+: 277 [M + Na]+

TABLE 26

PEx	Syn	Dat
127	PEx112	ESI+: 344
128	PEx112	ESI+: 344
129	PEx112	APCI/ESI+: 356
130	PEx112	ESI+: 356
131	PEx112	ESI+: 356
132	PEx113	ESI+: 352
133	PEx113	ESI+: 344
134	PEx111	ESI+: 275 [M + Na]+
135	PEx113	ESI+: 356
136	PEx113	ESI+: 356
137	PEx137	ESI+: 240
138	PEx137	ESI+: 240
139	PEx115	ESI+: 210
140	PEx115	ESI+: 210
141	PEx116	NMR($CDCl_3$): 1.55 (9H, s), 6.39 (1H, d, J = 16 Hz), 7.37 (1H, d, J = 5 Hz), 7.68 (1H, d, J = 5 Hz), 8.07 (1H, d, J = 16 Hz), 10.22 (1H, d, J = 1 Hz)
142	PEx5	ESI+: 319
143	PEx113	ESI+: 344
144	PEx104	ESI+: 253
145	PEx104	ESI+: 249
146	PEx104	ESI+: 253
147	PEx104	EI: 248
148	PEx104	EI: 252
149	PEx105	EI: 314
150	PEx105	EI: 310, 312
151	PEx105	ESI+: 315, 317
152	PEx105	EI: 310, 312
153	PEx105	ESI+: 337, 339 [M + Na]+
154	PEx106	ESI+: 446
155	PEx106	ESI+: 442

TABLE 27

PEx	Syn	Dat
156	PEx106	ESI+: 442
157	PEx106	ESI+: 446
158	PEx106	ESI+: 446

TABLE 27-continued

PEx	Syn	Dat
159	PEx106	ESI+: 428
160	PEx107	ESI+: 404
161	PEx107	ESI+: 404
162	PEx107	ESI+: 400
163	PEx107	ESI+: 400
164	PEx107	APCI/ESI+: 404

TABLE 28

PEx	Syn	Dat
165	PEx165	ESI−: 324[M + HCOO]−
166	PEx166	ESI+: 360 [M + Na]+
167	PEx167	ESI+: 438, 440 [M + Na]+
168a	PEx168	ESI+: 418 [M + Na]+
168b	PEx168	ESI+: 418 [M + Na]+
169a	PEx169	ESI+: 266
169b	PEx169	ESI+: 266
170	PEx170	ESI+: 531
171	PEx171	ESI+: 376 [M + Na]+
172	PEx172	ESI+: 166
173	PEx173	APCI/ESI+: 326
174	PEx174	ESI+: 326
175	PEx175	ESI+: 294
176	PEx176	ESI+: 192
177	Ex5	ESI+: 180
178	PEx178	APCI/ESI+: 212
179	PEx179	APCI/ESI+: 226
180	PEx180	APCI/ESI+: 266
181a	PEx 181	ESI+: 294 NMR($CDCl_3$): 1.43 (9H, brs), 2.50-2.59 (4H, m), 4.02 (4H, brs), 5.12 (1H, brs), 7.27-7.30 (1H, m), 7.35-7.43 (4H, m)
181b	PEx 181	ESI+: 294 NMR($CDCl_3$): 1.39 (9H, brs), 2.24-2.32 (4H, m), 2.64 (2H, brs), 4.37-4.43 (2H, m), 4.80 (1H, brs), 7.19-7.23 (1H, m), 7.32 (2H, t, J = 7.4 Hz), 7.41-7.43 (2H, m)
182	PEx182	ESI+: 382
183	PEx183	ESI+: 208
184	PEx184	APCI/ESI+: 343
185	PEx185	APCI/ESI+: 343
186	PEx186	APCI/ESI+: 222
187	PEx187	ESI+: 268
188	PEx188	ESI+: 268
189	PEx189	ESI+: 298
190	PEx190	ESI+: 312
191	PEx191	ESI+: 248
192	PEx192	ESI+: 234
193	PEx193	ESI+: 322
194a	PEx194	ESI+: 324
194b	PEx194	EI: 205
195	PEx195	EI: 188

TABLE 29

PEx	Syn	Dat
196	PEx196	ESI+: 335
197	PEx197	ESI+: 194
198	PEx198	ESI+: 168
199	PEx199	ESI+: 268
200	PEx200	ESI+: 322
201	PEx201	ESI+: 104
202	Ex1	ESI+: 406
203	Ex19	ESI+: 196
204	Ex20	APCI/ESI+: 209
205	Ex20	APCI/ESI+: 209
206	Ex5	ESI+: 235
207	Ex5	ESI+: 235
208	Ex5	ESI+: 236
209	Ex5	ESI+: 236
210	Ex5	ESI+: 222

TABLE 29-continued

PEx	Syn	Dat
211	Ex5	ESI+: 166
212	Ex5	ESI+: 166
213	Ex5	ESI+: 194
214	Ex5	ESI+: 180
215	Ex5	ESI+: 180
216	Ex6	ESI+: 298
217	Ex9	CI+: 290
218	PEx1	ESI+: 363
219	PEx1	ESI+: 365
220	PEx10	ESI+: 436
221	PEx11	NMR($CDCl_3$): 1.22-1.74 (22H, m), 2.16 (1H, dd, J = 9.8 Hz, 15.4 Hz), 2.35 (1H, dd, J = 3.5 Hz, 15.4 Hz), 3.03-3.13 (1H, m)
222	PEx188	ESI+: 298
223	PEx112	ESI+: 292
224a	PEx113	ESI+: 298 NMR($CDCl_3$): 1.24 (9H, s), 3.65 (1H, d, J = 7.0 Hz), 3.82 (3H, s), 5.03 (1H, d, J = 4.7 Hz), 5.30 (1H, dd, J = 4.9, 7.0 Hz), 6.96 (1H, d, J = 8.1 Hz), 7.01 (1H, t, J = 7.5 Hz), 7.25-7.31 (1H, m), 7.48 (1H, d, J = 7.5 Hz)
224b	PEx113	ESI+: 298 NMR($CDCl_3$): 1.18 (9H, s), 3.50 (1H, d, J = 9.1 Hz), 3.82 (3H, s), 5.21 (1H, d, J = 8.4 Hz), 5.31 (1H, t, J = 8.7 Hz), 6.93 (1H, d, J = 8.2 Hz), 7.01 (1H, t, J = 7.5 Hz), 7.24-7.30 (1H, m), 7.57 (1H, d, J = 7.3 Hz)
225a	PEx113	ESI+: 298 NMR($CDCl_3$): 1.24 (9H, s), 3.68 (1H, d, J = 7.1 Hz), 3.82 (3H, s), 5.03 (1H, d, J = 4.8 Hz), 5.30 (1H, dd, J = 4.8, 7.0 Hz), 6.95 (1H, d, J = 8.1 Hz), 7.00 (1H, dt, J = 0.8, 7.5 Hz), 7.26-7.31 (1H, m), 7.48 (1H, d, J = 7.5 Hz)
225b	PEx113	ESI+: 298 NMR($CDCl_3$): 1.18 (9H, s), 3.51 (1H, d, J = 9.1 Hz), 3.82 (3H, s), 5.21 (1H, d, J = 8.3 Hz), 5.31 (1H, t, J = 8.7 Hz), 6.93 (1H, d, J = 8.1 Hz), 7.01 (1H, dt, J = 0.9, 7.5 Hz), 7.27 (1H, dt, J = 1.3, 7.8 Hz), 7.57 (1H, d, J = 7.5 Hz)

TABLE 30

PEx	Syn	Dat
226	PEx114	ESI+: 208
227	PEx12	ESI+: 337, 339
228	PEx137	ESI+: 208
229	PEx137	ESI+: 194
230	PEx137	ESI+: 206
231	PEx137	ESI+: 194
232	PEx137	ESI+: 194
233	PEx137	ESI+: 194
234	PEx137	ESI+: 194
235	PEx168	ESI+: 356[M + Na]+
236	PEx169	ESI+: 180
237a	PEx170, 171	ESI+: 324
237b	PEx170, 171	ESI+: 324
238	PEx171	ESI+: 382
239	PEx171	ESI+: 376[M + Na]+
240	PEx172	ESI+: 166
241	PEx174	ESI+: 326
242	PEx174	ESI+: 326
243	PEx176, Ex16	ESI+: 192
244	PEx176, Ex16	ESI+: 192
245	PEx176, Ex16	ESI+: 192
246	PEx178	ESI+: 234 (M + Na)+
247	PEx179	APCI/ESI+: 226
248	PEx179	ESI+: 326
249	PEx180	APCI/ESI+: 274 [M + Na]+
250	PEx180	APCI/ESI+: 274 [M + Na]+
251	PEx178	ESI+: 193
252	PEx180	CI+: 233
253	PEx180	APCI/ESI+: 266
254	PEx181	ESI+: 324
255	PEx184	ESI+: 290

TABLE 30-continued

PEx	Syn	Dat
256	PEx186	APCI/ESI+: 222
257	PEx186	ESI+: 208
258	PEx186	APCI/ESI+: 222

TABLE 31

PEx	Syn	Dat
259	PEx187	ESI+: 238
260	PEx188	ESI+: 298
261	PEx189	ESI+: 312
262	PEx189	ESI+: 310
263	PEx199	ESI+: 260
264	PEx200	ESI+: 350
265	PEx200	ESI+: 336
266	PEx201	ESI+: 132
267	PEx201	ESI+: 118
268	PEx22	NMR(DMSO-d_6): 1.52 (6H, s), 3.60 (3H, s), 4.03 (2H, s), 7.28-7.42 (3H, m), 7.45 (1H, s), 8.10-8.35 (3H, br)
269	PEx26	ESI+: 335
270	PEx27	ESI+: 336
271	PEx27	ESI+: 336
272	PEx5	ESI+: 335
273	PEx5	ESI+: 337
274	PEx5	APCI/ESI+: 238
275	PEx5	APCI/ESI+: 238
276	PEx5	ESI+: 175
277	PEx9	NMR($CDCl_3$): 1.29-1.82 (21H, m), 2.24-2.36 (1H, m), 5.67 (1H, dd, J = 1.2 Hz, 15.7 Hz), 6.85 (1H, dd, J = 7.6 Hz, 15.7 Hz)
278	Ex5	ESI+: 194 NMR(DMSO-d_6): 2.22 (2H, dd, J = 4.2, 14.8 Hz), 2.38 (2H, dd, J = 6.5, 14.8 Hz), 4.09-4.14 (2H, m), 4.80-5.60 (2H, br), 7.33-7.38 (1H, m), 7.43 (2H, t, J = 7.2 Hz), 7.47-7.51 (2H, m), 8.34 (3H, brs)
279	Ex5	ESI+: 194 NMR(DMSO-d_6): 2.21 (2H, dd, J = 5.7, 14.6 Hz), 2.31 (2H, dd, J = 6.1, 14.6 Hz), 4.23 (2H, t, J = 4.4 Hz), 4.81 (2H, brs), 7.32-7.36 (1H, m), 7.43 (2H, t, J = 7.4 Hz), 7.53-7.57 (2H, m), 8.46 (3H, brs)

TABLE 32

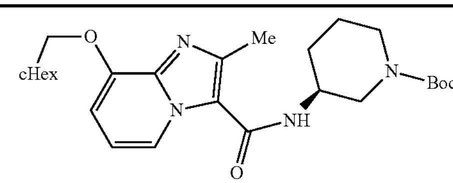
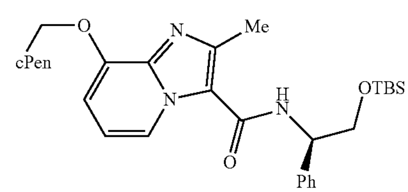
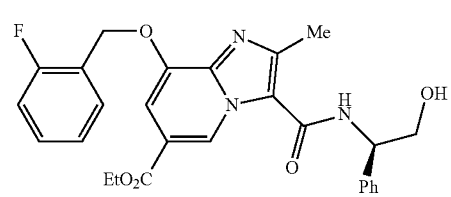
Ex	Str
1	
2	
3	

TABLE 32-continued

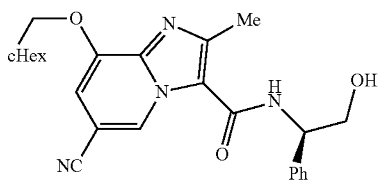
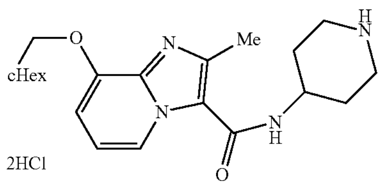
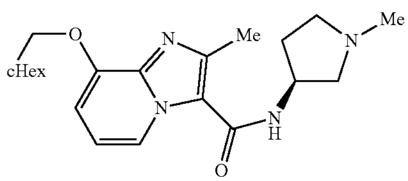
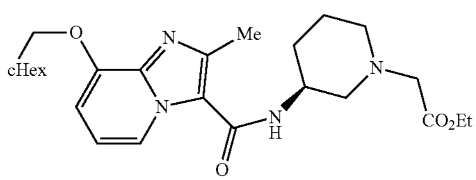
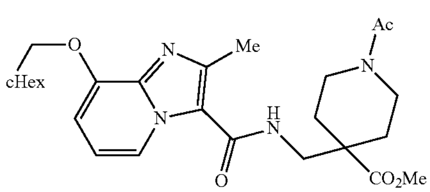
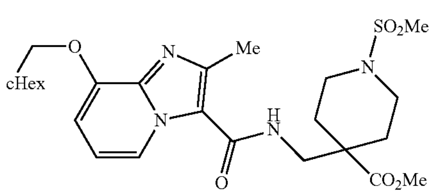
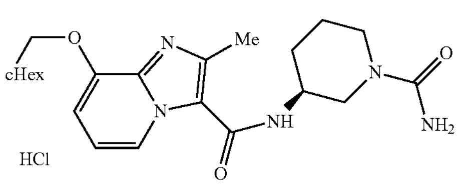
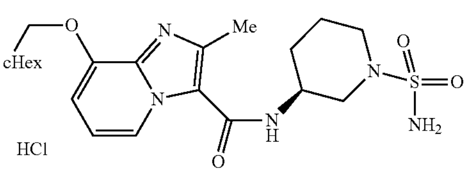
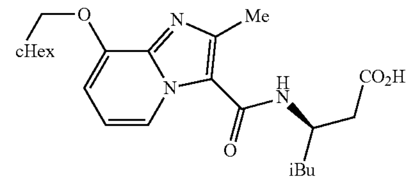
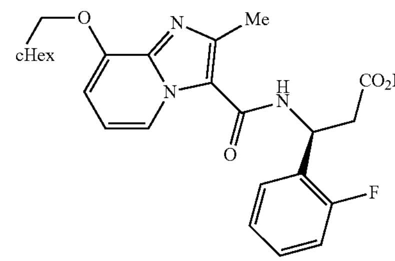
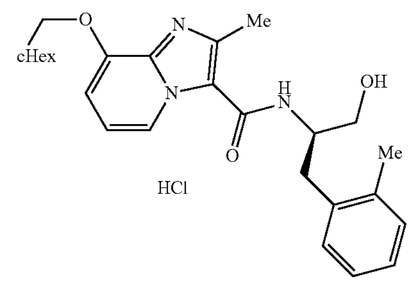
Ex	Str
4	
5	
6	
7	
8	
9	
10	
11	
12	
13	
14	

TABLE 33

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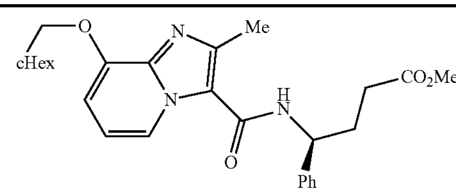
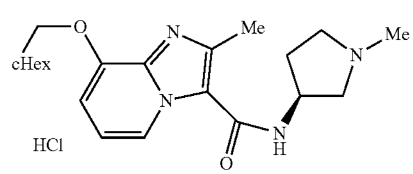
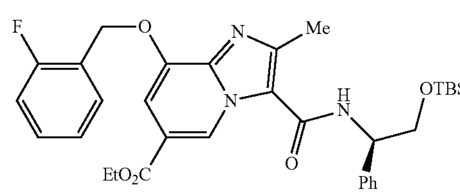
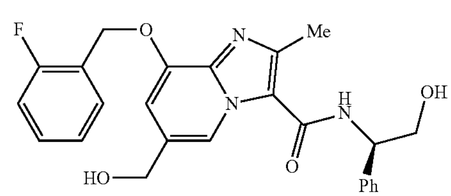
15	
16	
17	
18	

TABLE 33-continued

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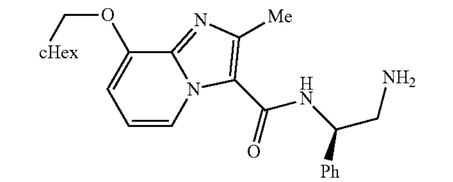
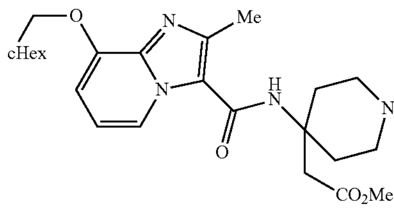
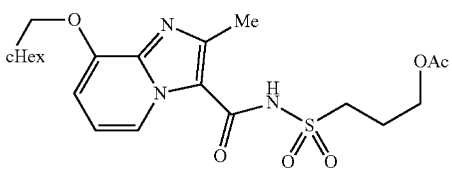
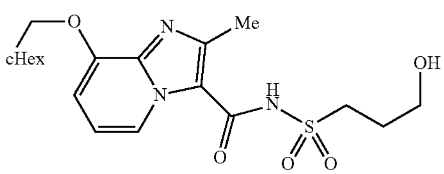
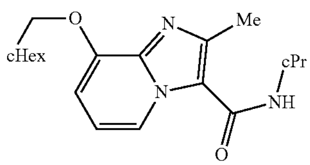
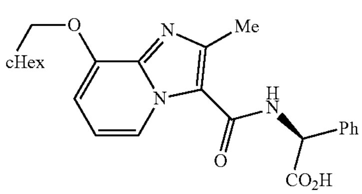
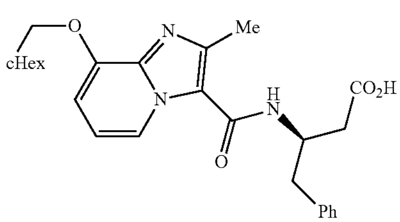
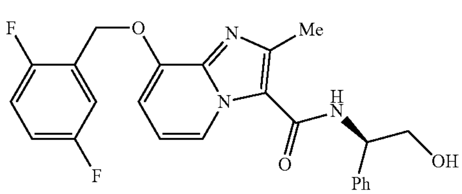
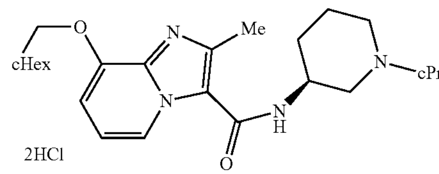
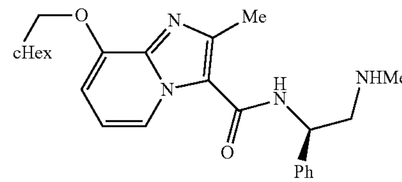
19	
20	
21	
22	
23	
24	
25	
26	
27	 2HCl
28	

TABLE 34

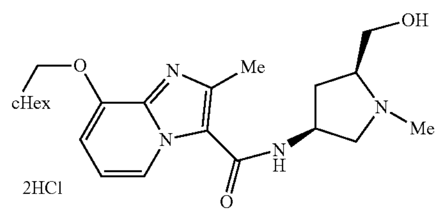
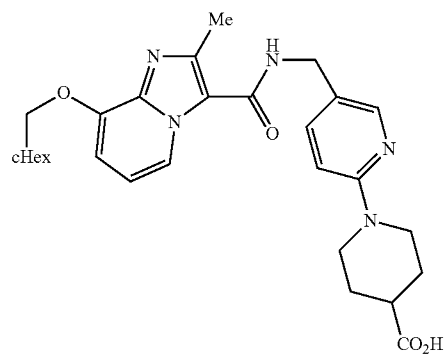
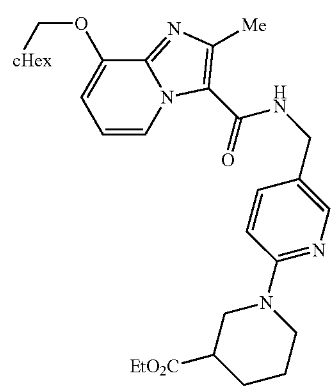
Ex	Str
29	 2HCl
30	
31	

TABLE 34-continued

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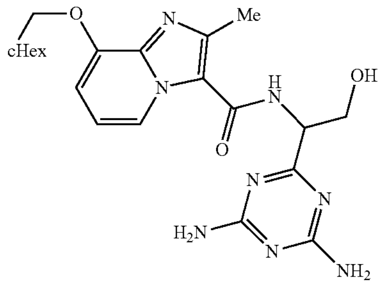
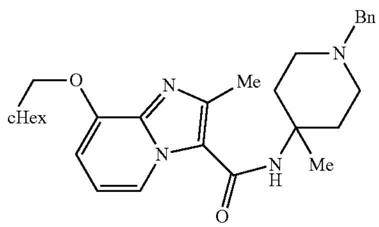
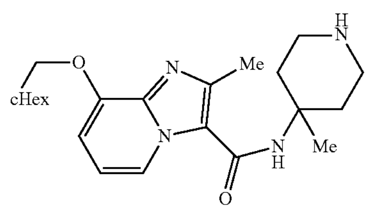
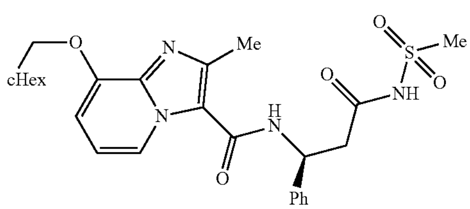
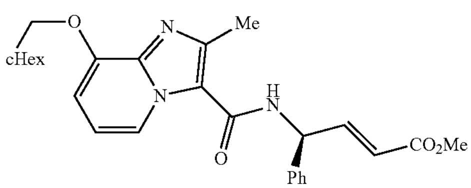
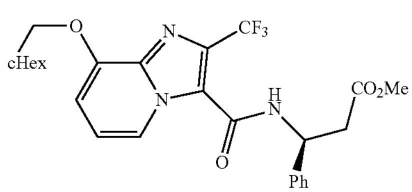
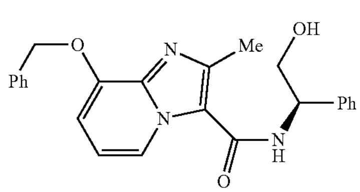
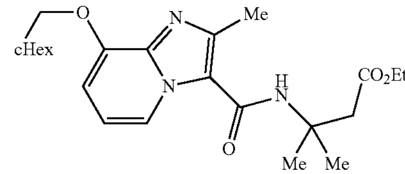
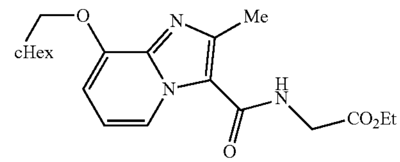
32	
33	
34	
35	
36	
37	
38	
39	
40	

TABLE 35

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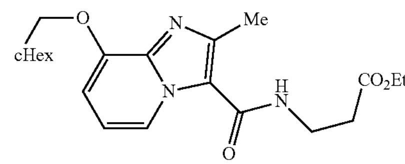
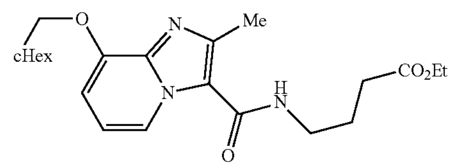
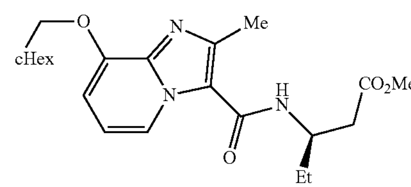
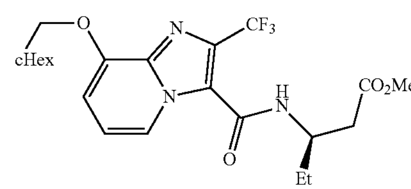
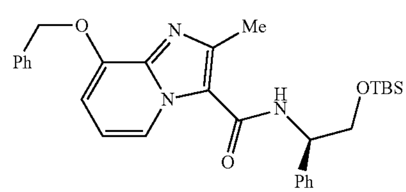
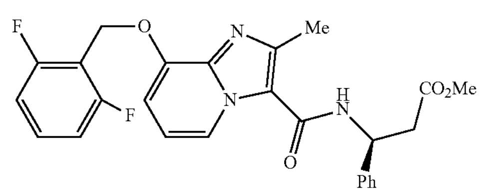
41	
42	
43	
44	
45	
46	

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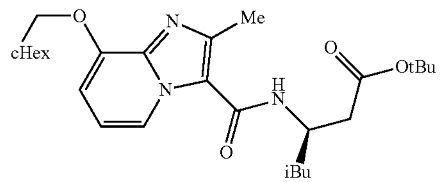
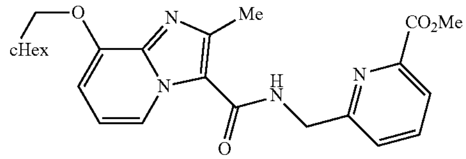
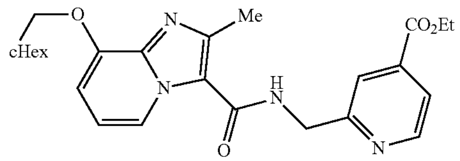
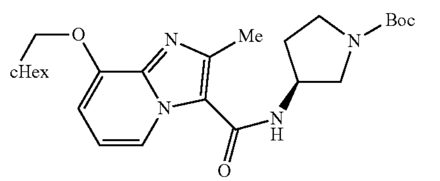
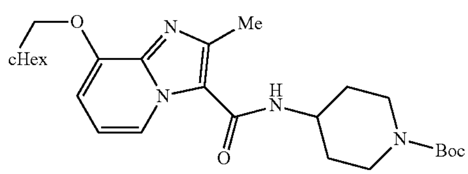
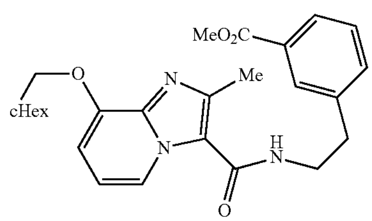
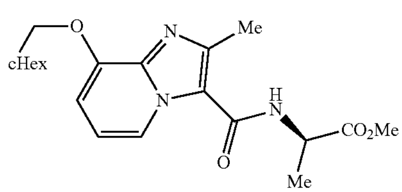
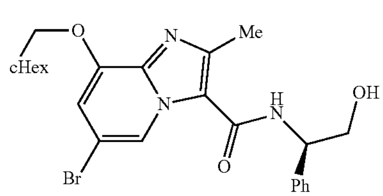
47	
48	
49	
50	
51	
52	
53	
54	

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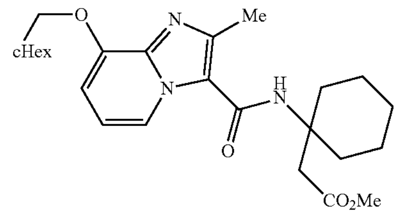
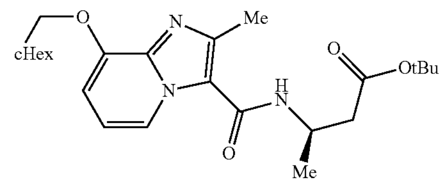
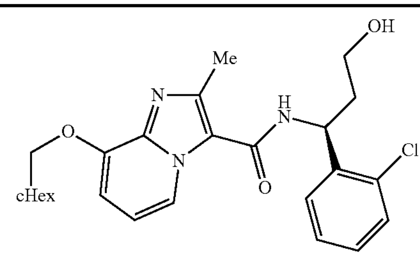
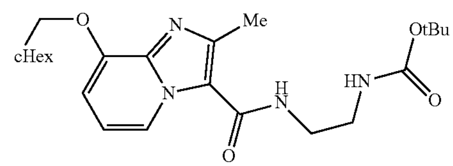
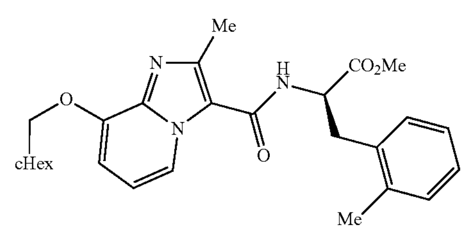
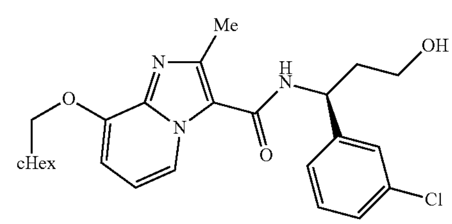
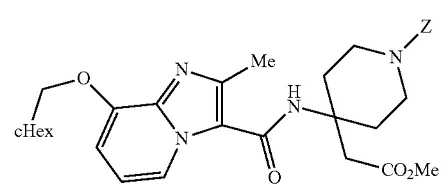
55	
56	

TABLE 36

Ex	Str
57	
58	
59	
60	
61	

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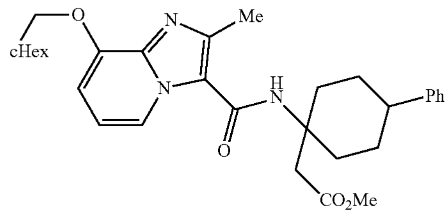
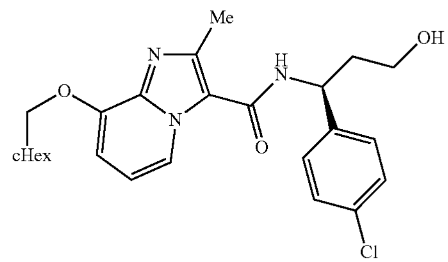
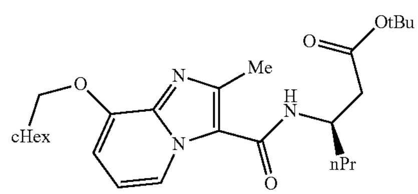
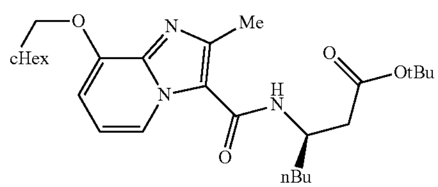
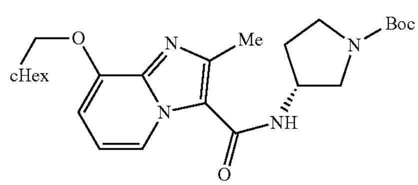
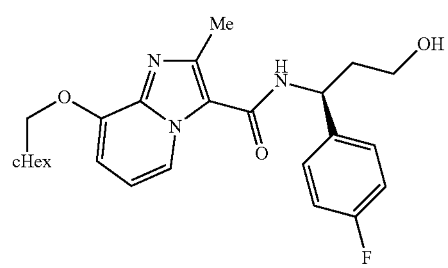
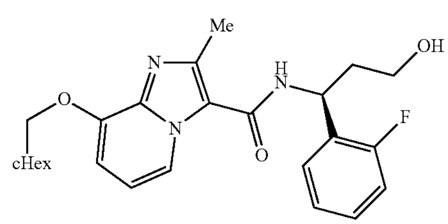
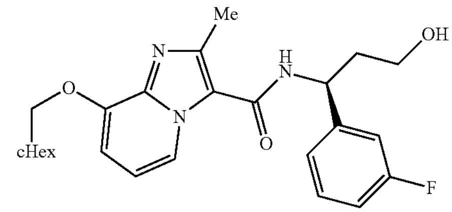
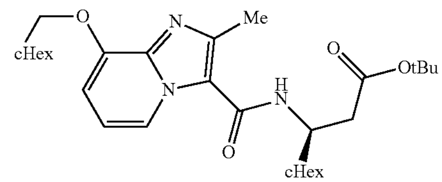
62	
63	
64	
65	
66	
67	
68	
69	
70	

TABLE 37

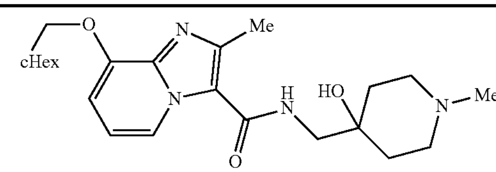
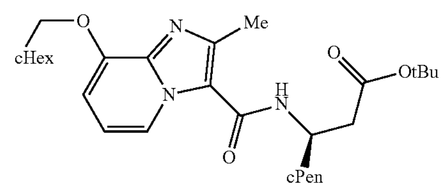
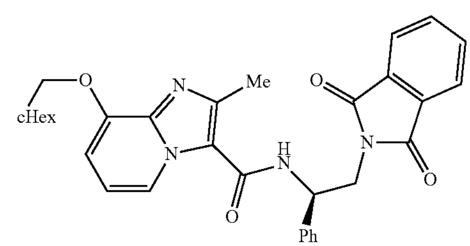
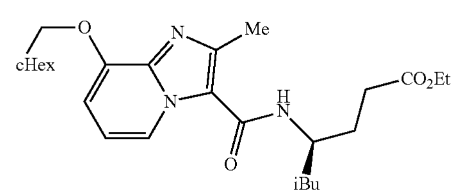
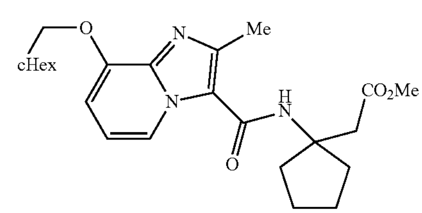
Ex	Str
71	
72	
73	
74	
75	

TABLE 37-continued

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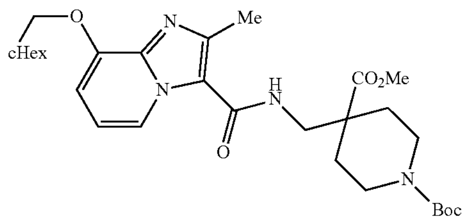
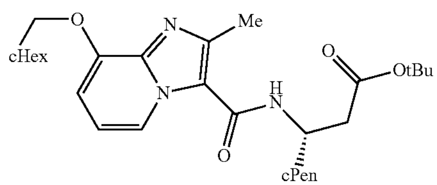
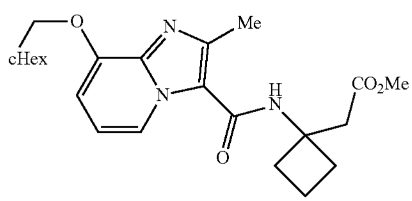
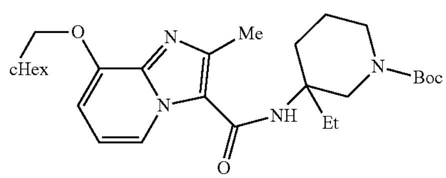
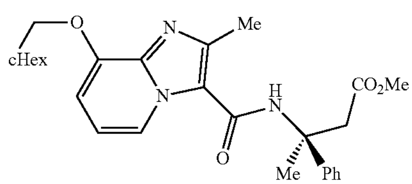
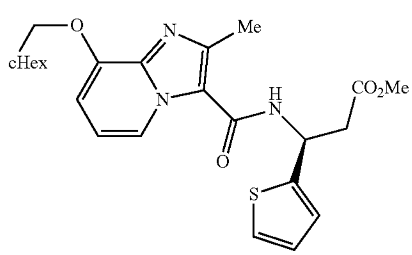
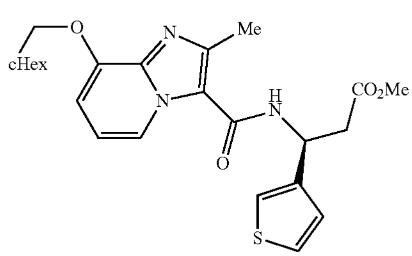
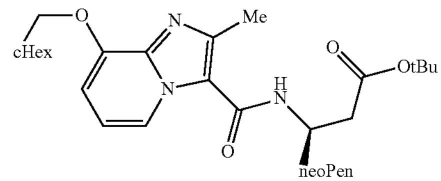
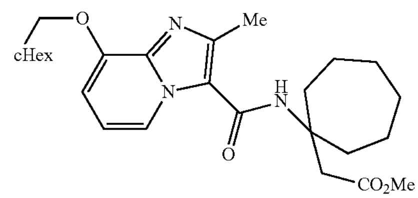
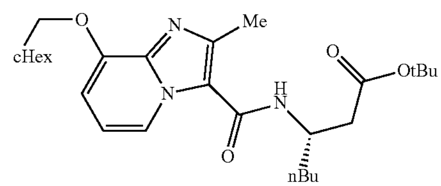
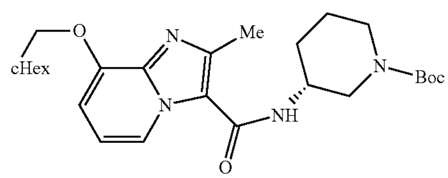
76	
77	
78	
79	
80	
81	
82	
83	
84	
85	
86	

TABLE 38

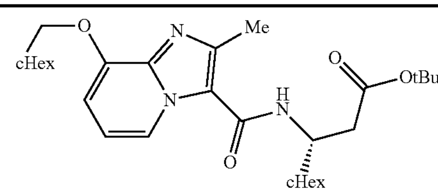
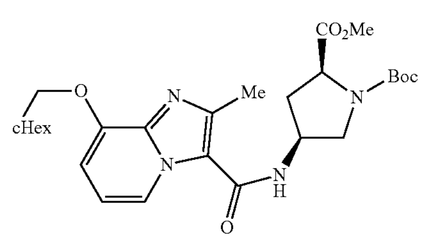
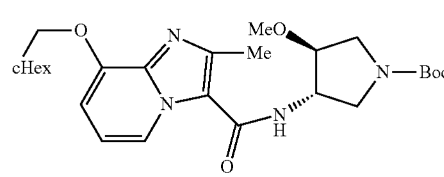
Ex	Str
87	
88	
89	

TABLE 38-continued

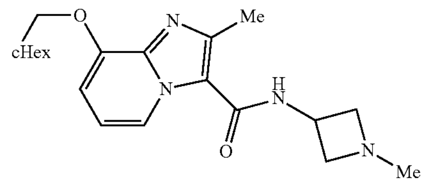
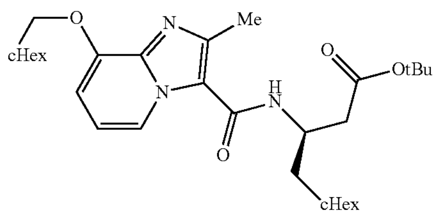
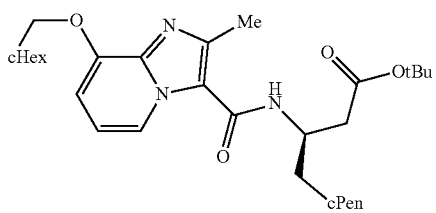
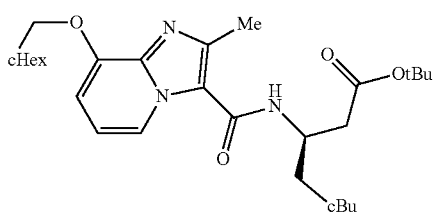
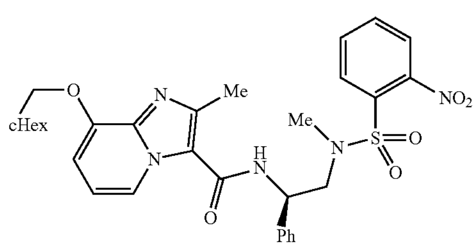
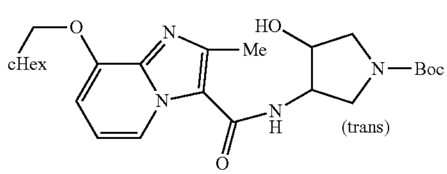
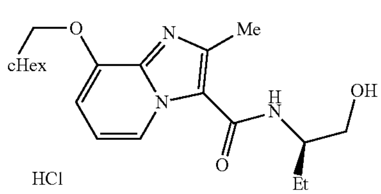
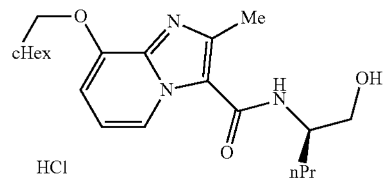
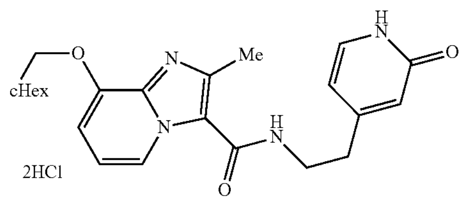
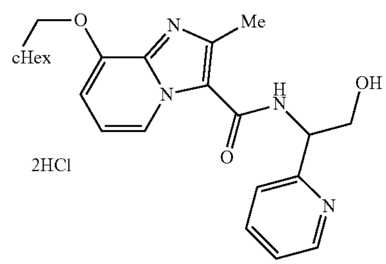
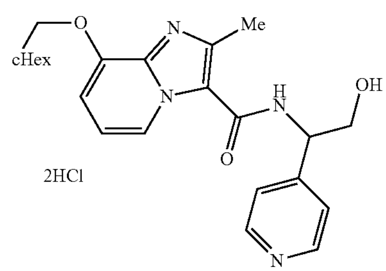
Ex	Str
90	
91	
92	
93	
94	
95	
96	 HCl
97	 HCl
98	 2HCl
99	 2HCl
100	 2HCl

TABLE 39

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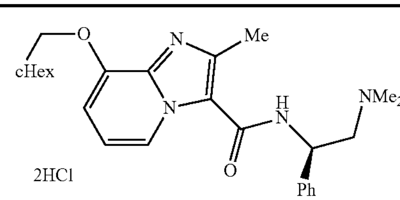
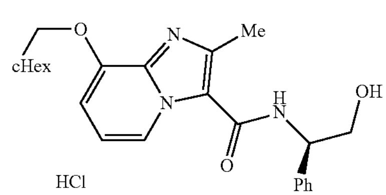
101	 2HCl
102	 HCl

TABLE 39-continued

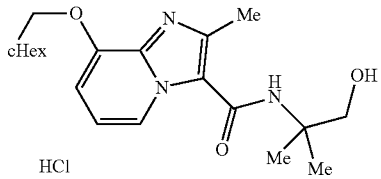
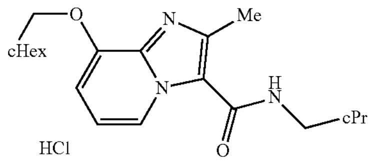
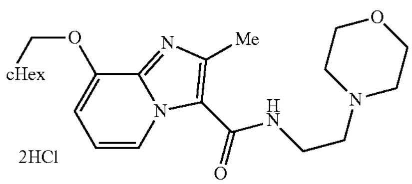
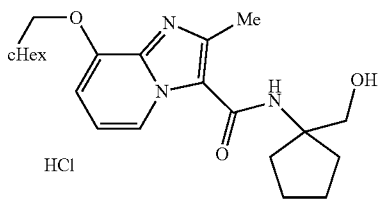
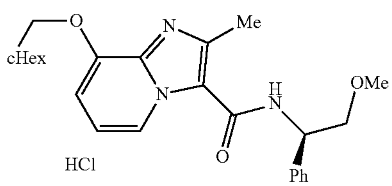
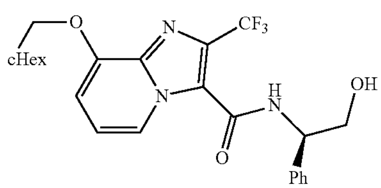
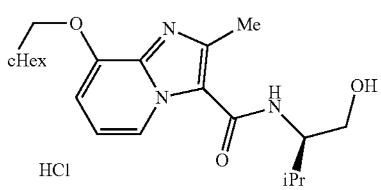
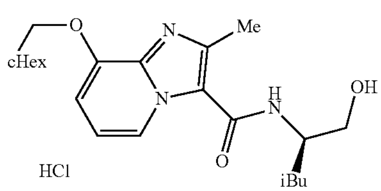
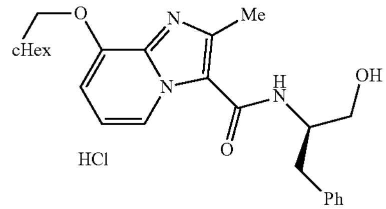
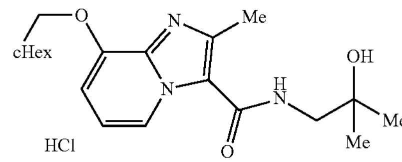
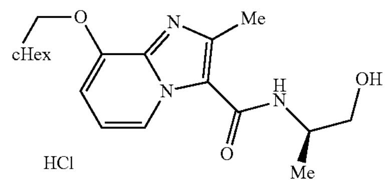
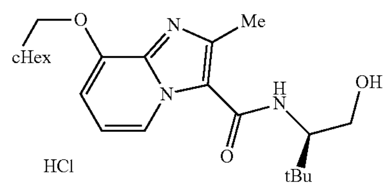
Ex	Str
103	 HCl
104	 HCl
105	 2HCl
106	 HCl
107	 HCl
108	
109	 HCl
110	 HCl
111	 HCl
112	 HCl
113	 HCl
114	 HCl

TABLE 40

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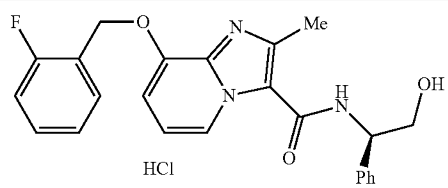
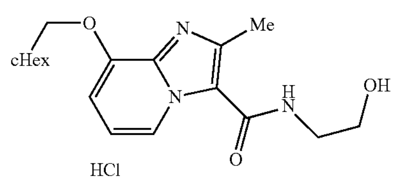
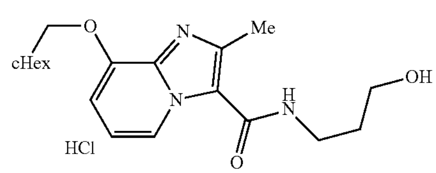
115	 HCl
116	 HCl
117	 HCl

TABLE 40-continued

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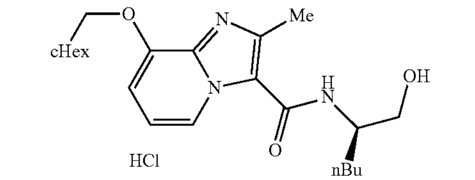
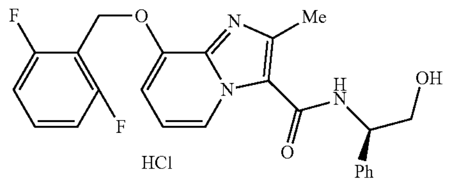
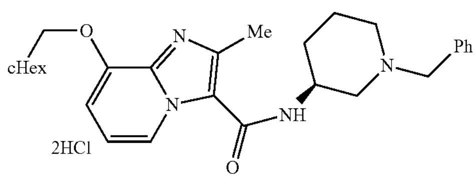
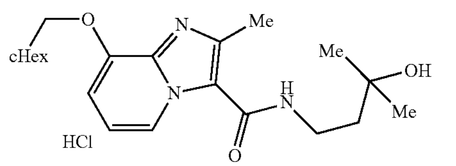
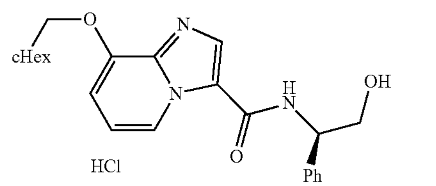
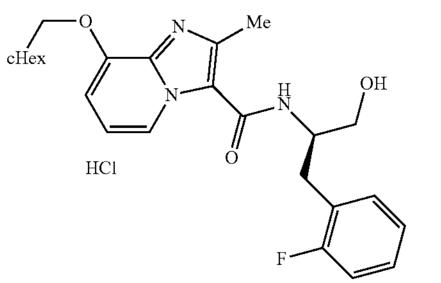
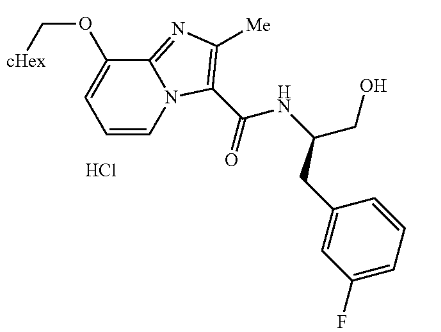
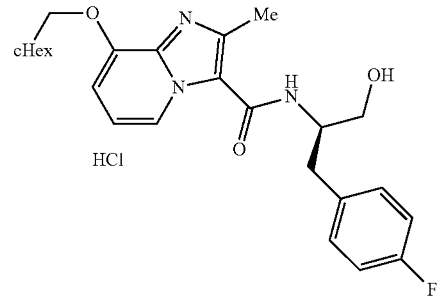
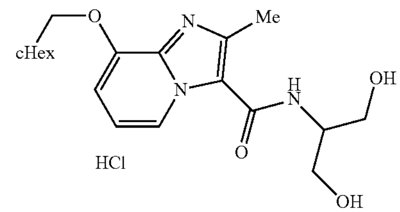
118	
119	
120	
121	
122	
123	
124	
125	
126	

TABLE 41

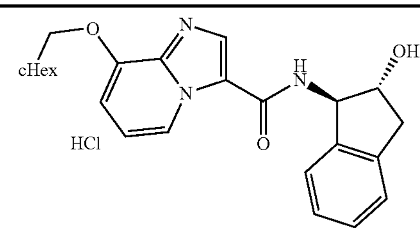
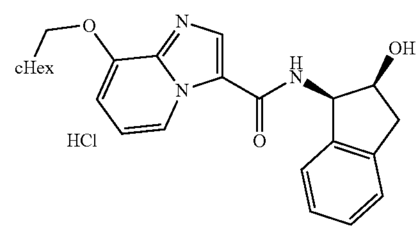
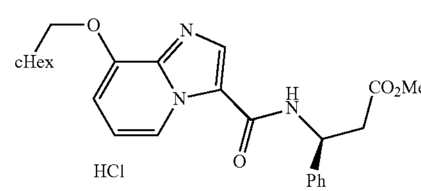
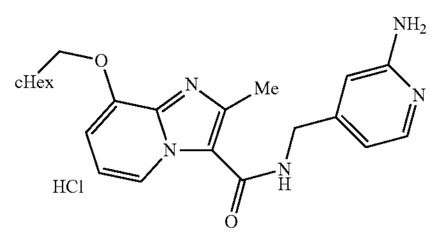
Ex	Str
127	
128	
129	
130	

TABLE 41-continued

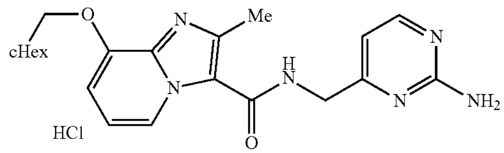
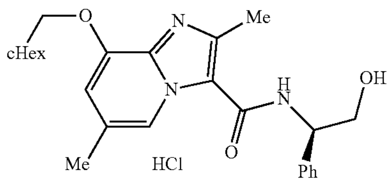
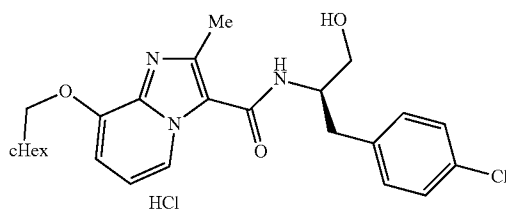
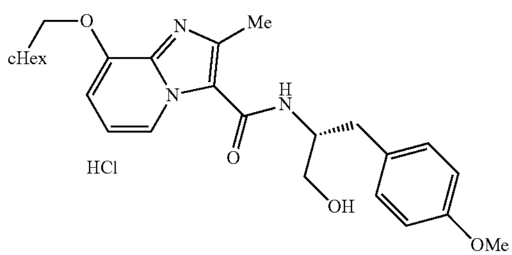
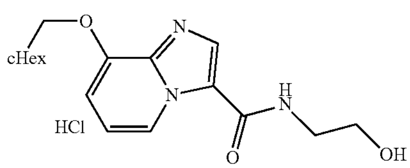
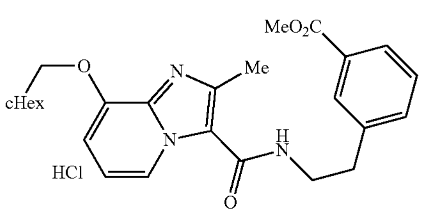
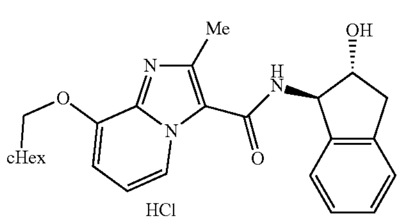
Ex	Str
131	
132	
133	
134	
135	
136	
137	

TABLE 41-continued

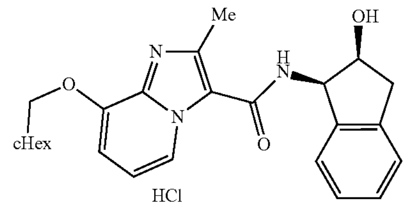
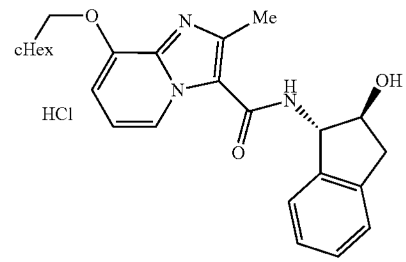
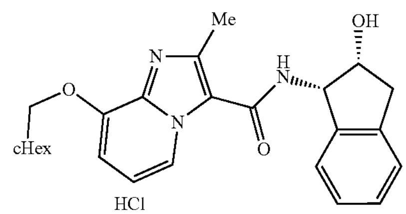
Ex	Str
138	
139	
140	

TABLE 42

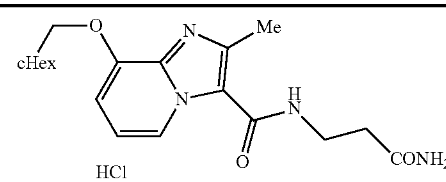
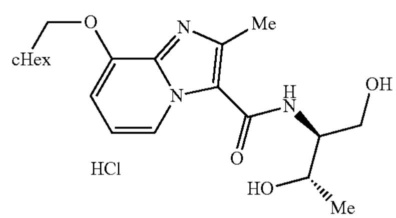
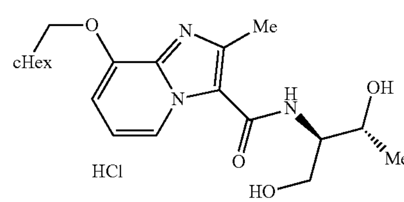
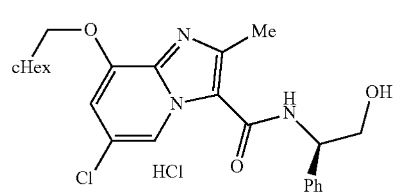
Ex	Str
141	
142	
143	
144	

TABLE 42-continued

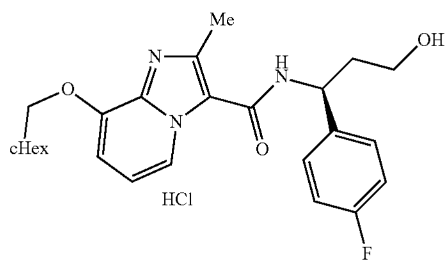
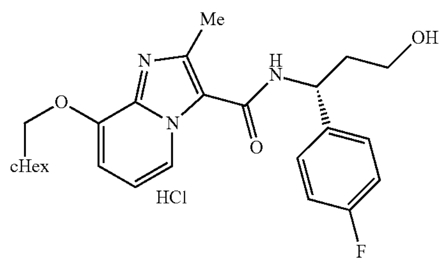
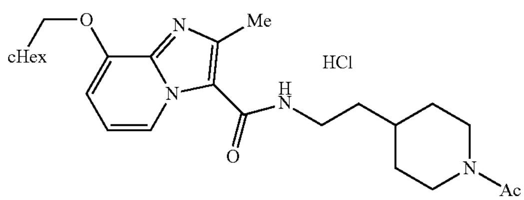
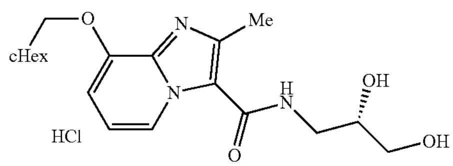
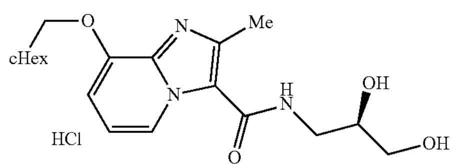
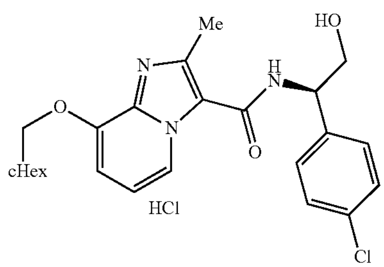
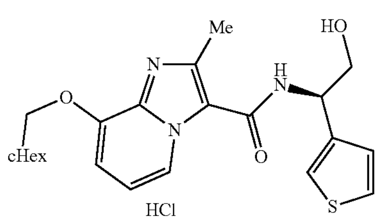
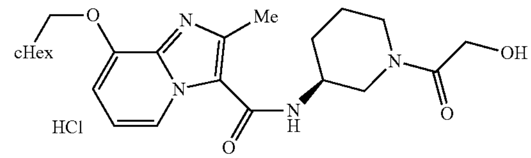
Ex	Str
145	
146	
147	
148	
149	
150	
151	
152	

TABLE 43

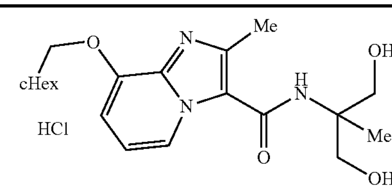
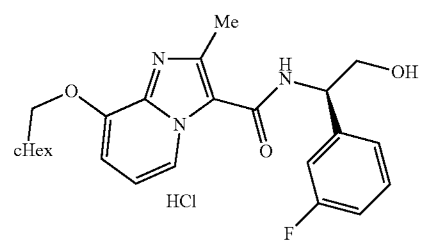
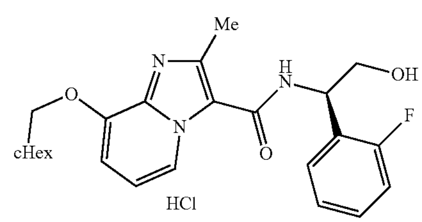
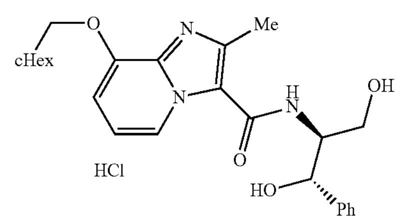
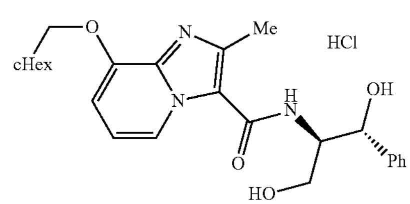
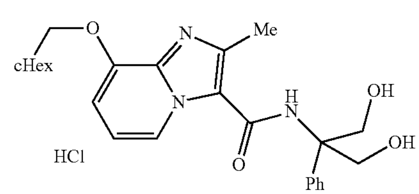
Ex	Str
153	
154	
155	
156	
157	
158	

TABLE 43-continued

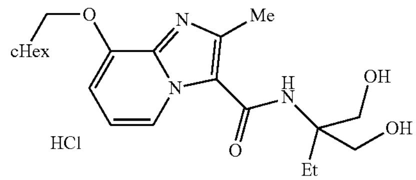
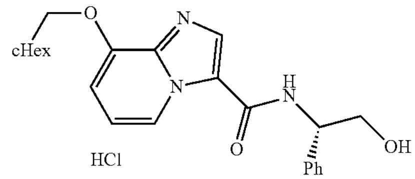
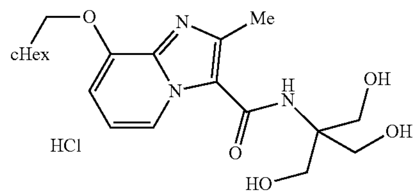
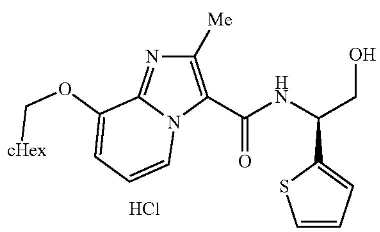
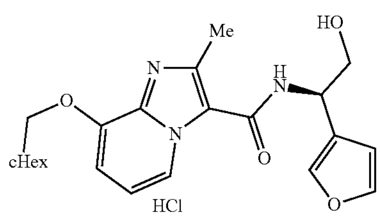
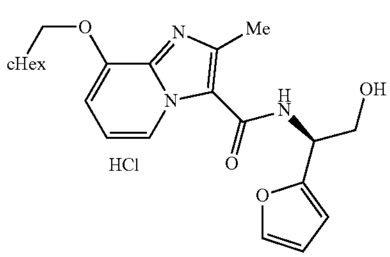
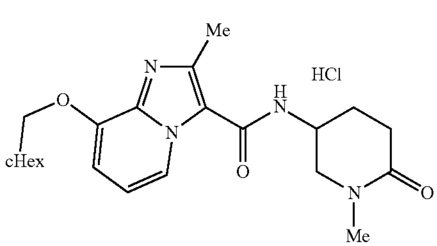
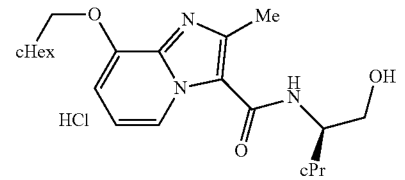
Ex	Str
159	
160	
161	
162	
163	
164	
165	
166	

TABLE 44

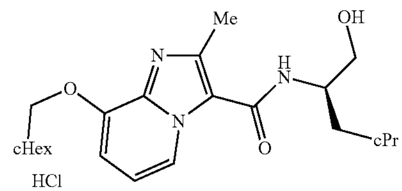
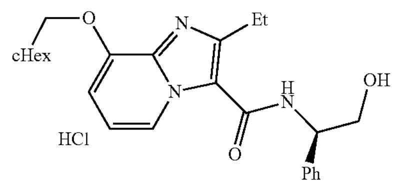
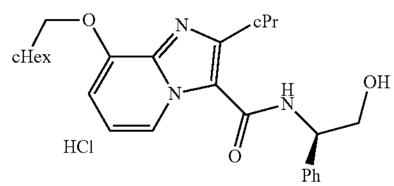
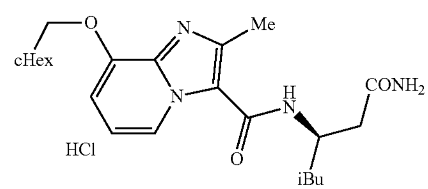
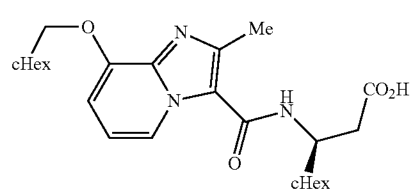
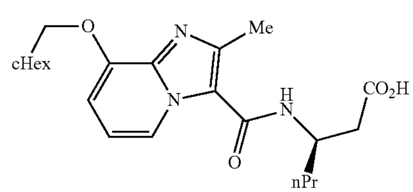
Ex	Str
167	
168	
169	
170	
171	
172	

TABLE 44-continued

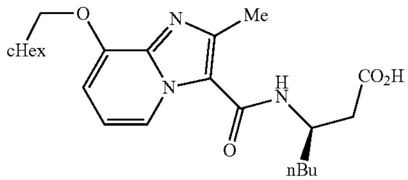
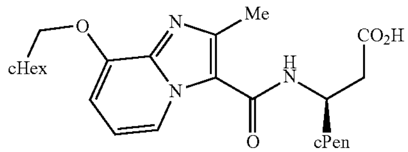
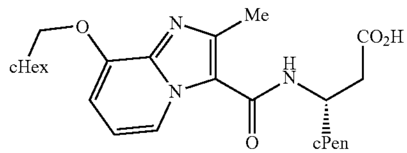
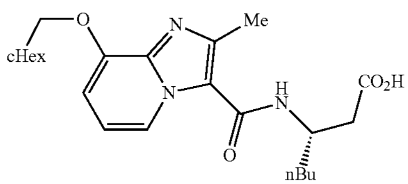
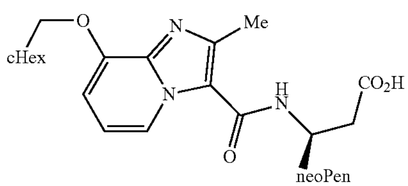
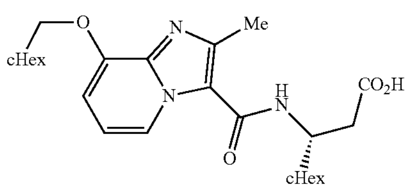
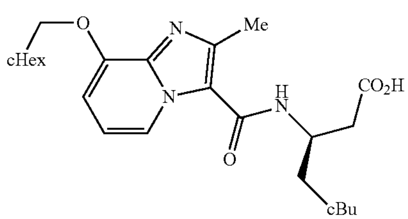
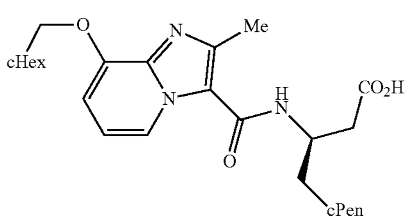
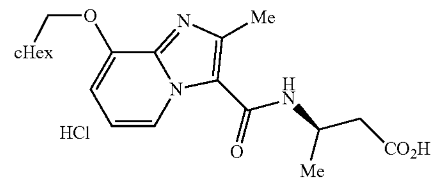
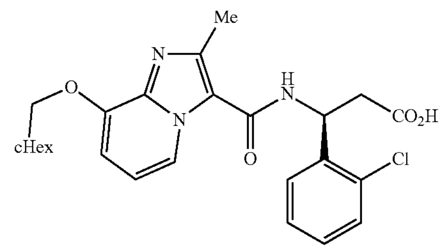
Ex	Str
173	
174	
175	
176	
177	
178	
179	
180	
181	
182	

TABLE 45

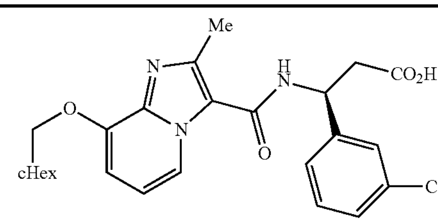
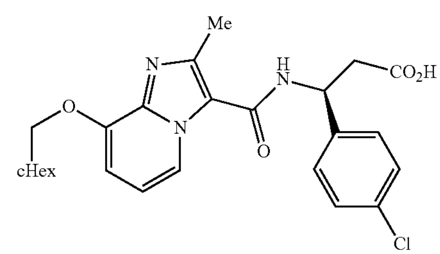
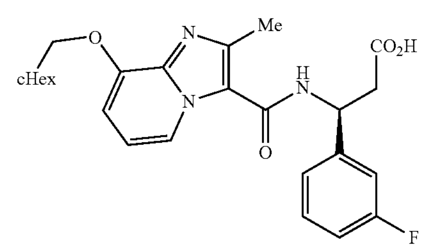
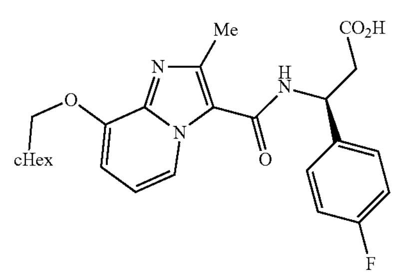
Ex	Str
183	
184	
185	
186	

TABLE 45-continued

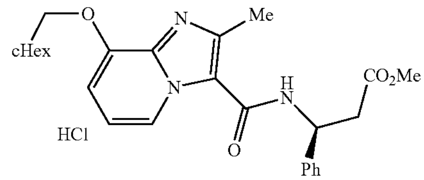
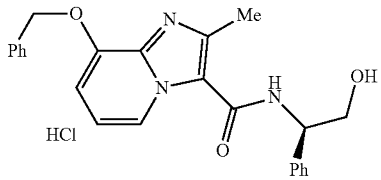
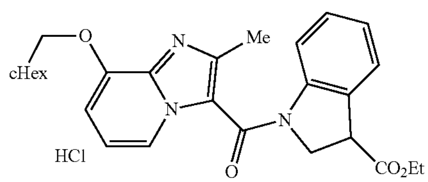
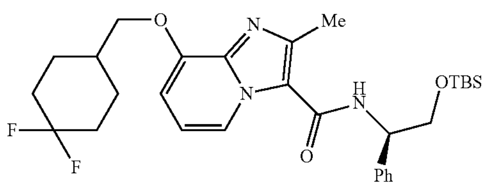
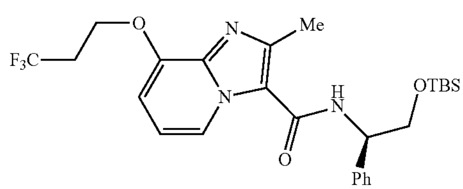
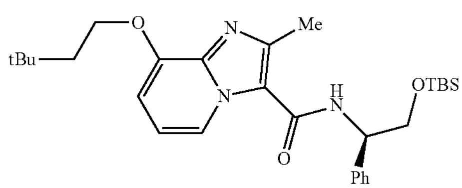
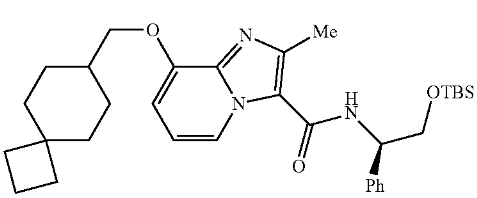
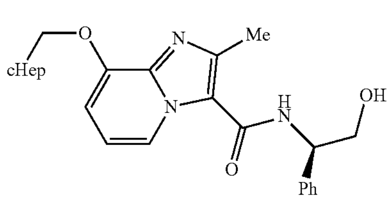
Ex	Str
187	
188	
189	
190	
191	
192	
193	
194	

TABLE 46

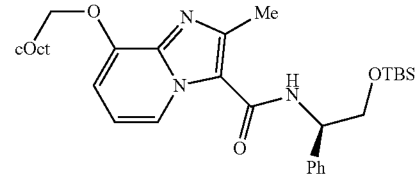
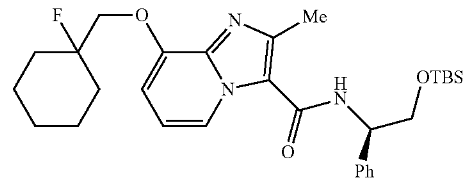
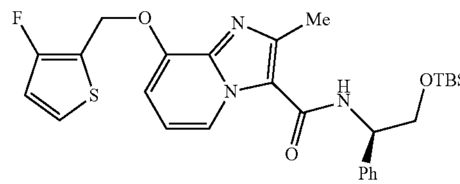
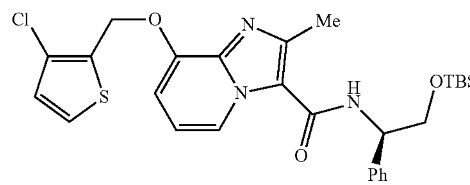
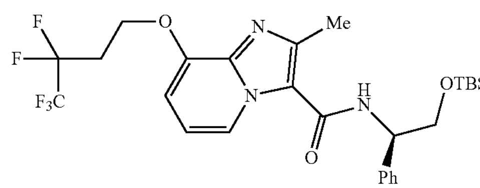
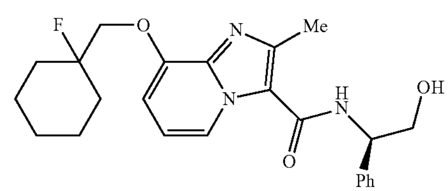
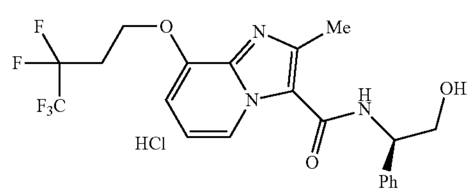
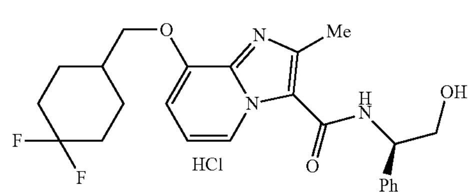
Ex	Str
195	
196	
197	
198	
199	
200	
201	
202	

TABLE 46-continued

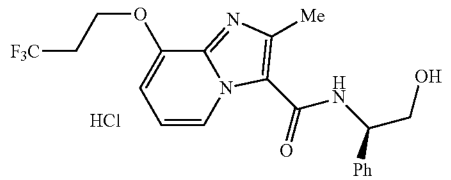
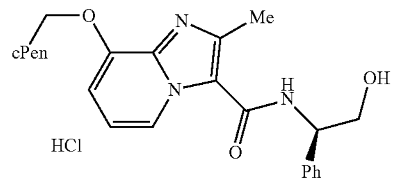
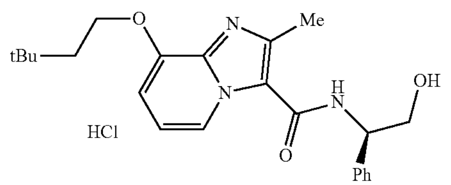
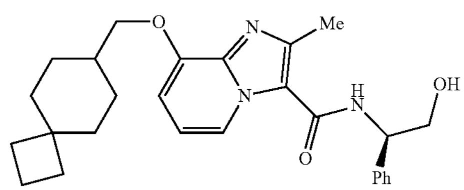
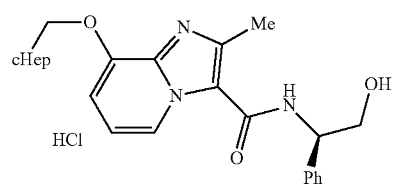
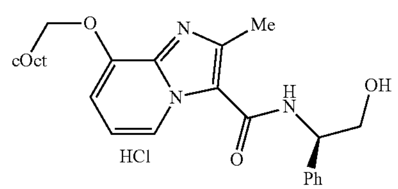
Ex	Str
203	
204	
205	
206	
207	
208	

TABLE 47

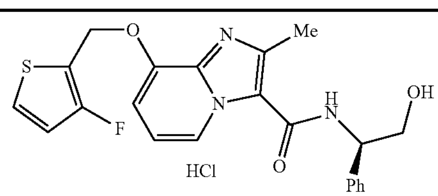
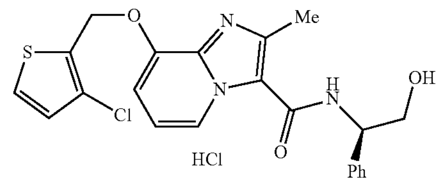
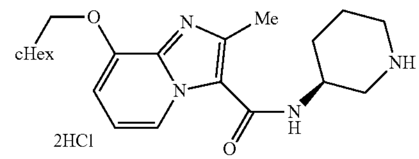
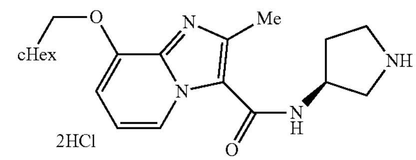
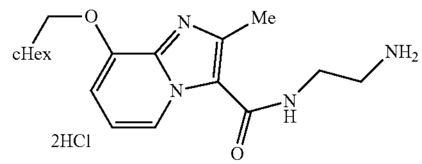
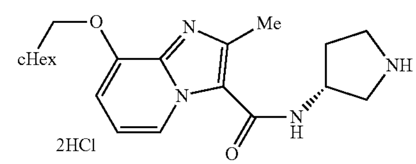
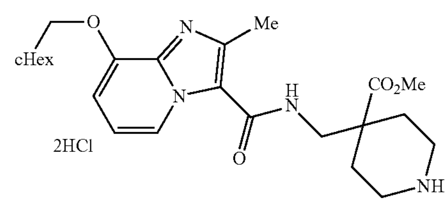
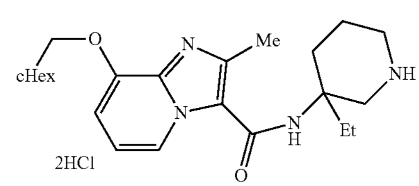
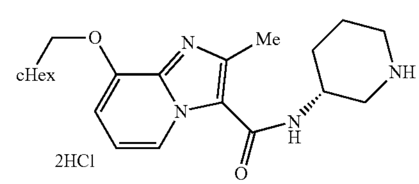
Ex	Str
209	
210	
211	
212	
213	
214	
215	
216	
217	

TABLE 47-continued

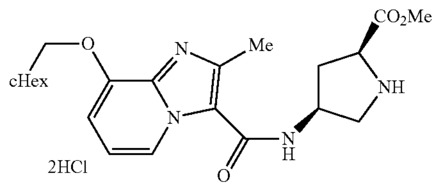
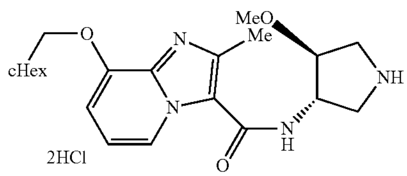
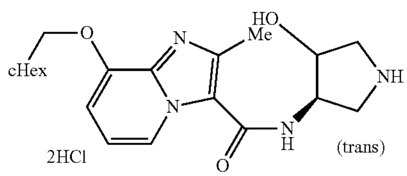
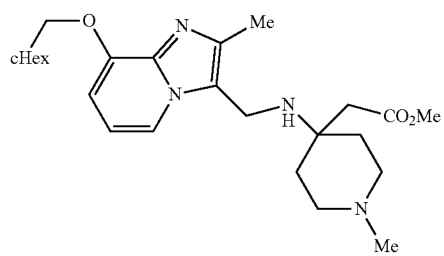
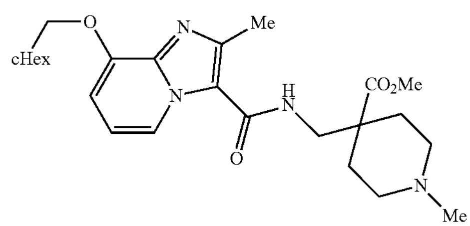
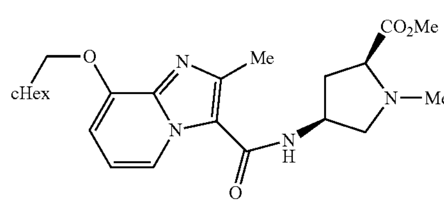
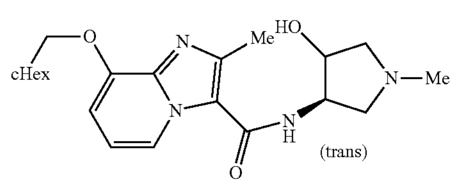
Ex	Str
218	
219	
220	
221	
222	
223	
224	

TABLE 48

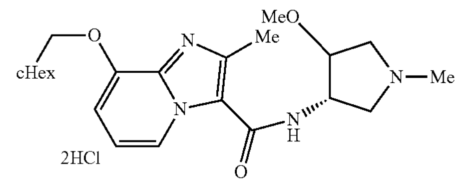
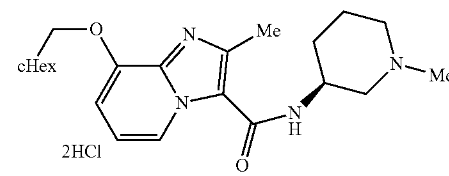
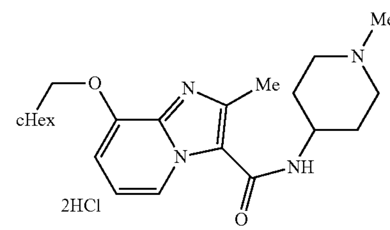
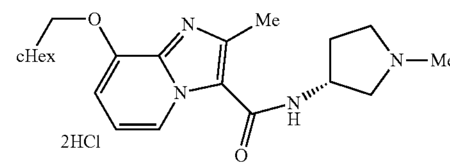
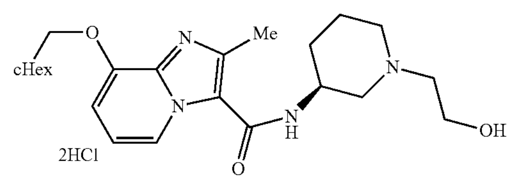
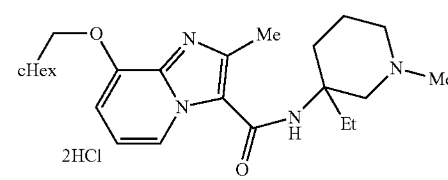
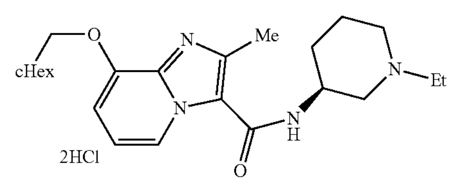
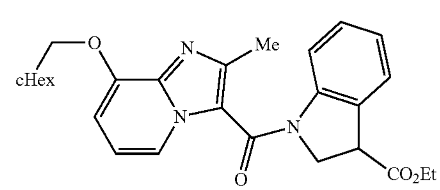
Ex	Str
225	
226	
227	
228	
229	
230	
231	
232	

TABLE 48-continued

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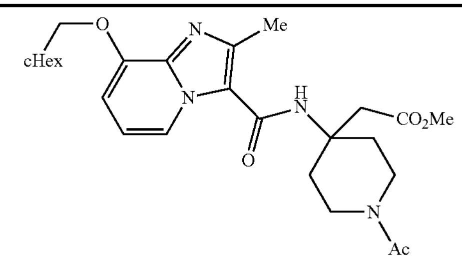
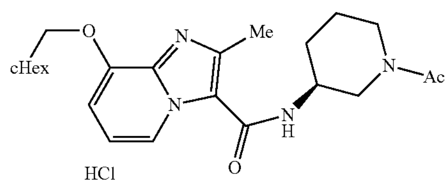
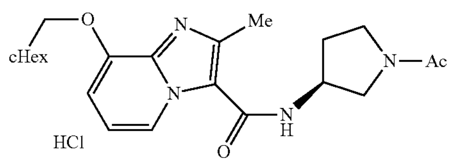
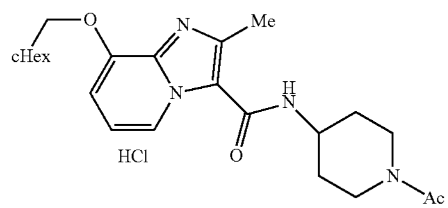
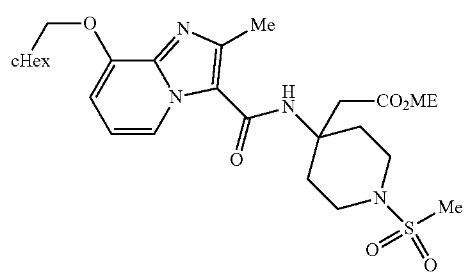
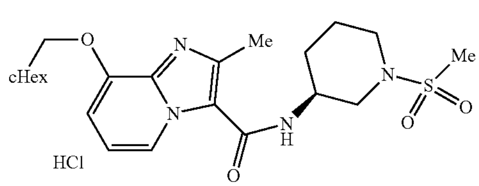
233	
234	
235	
236	
237	
238	

TABLE 49

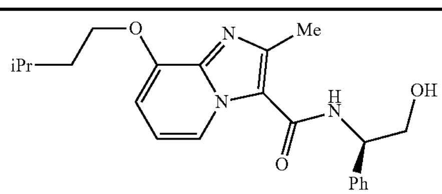
Ex	Str
239	

TABLE 49-continued

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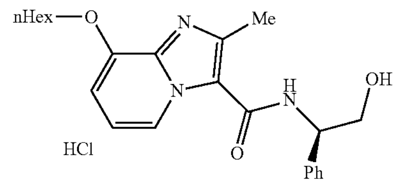
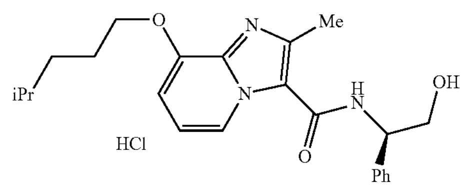
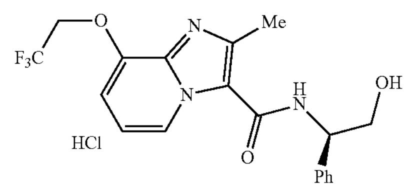
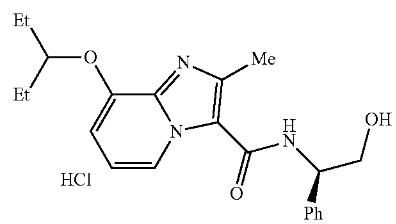
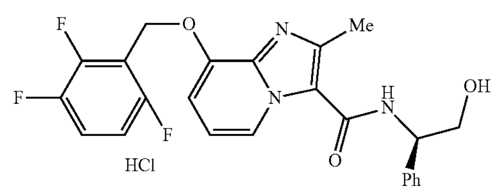
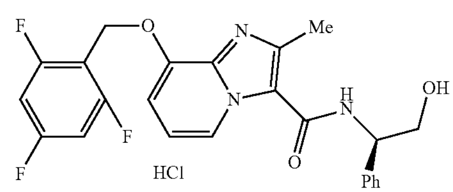
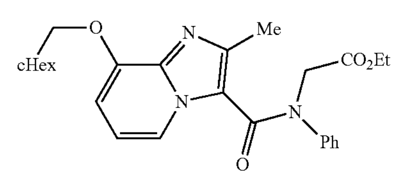
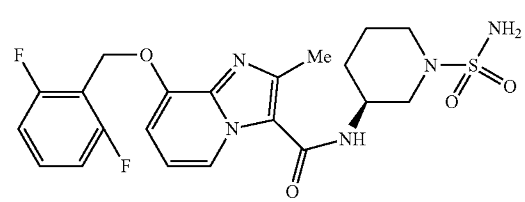
240	
241	
242	
243	
244	
245	
246	
247	

TABLE 49-continued

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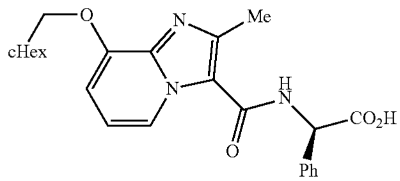
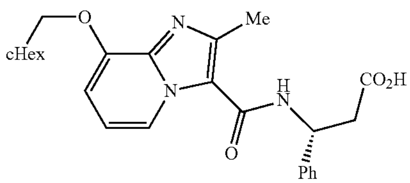
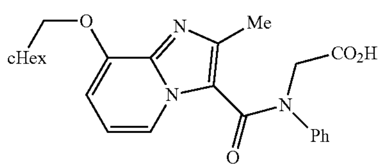
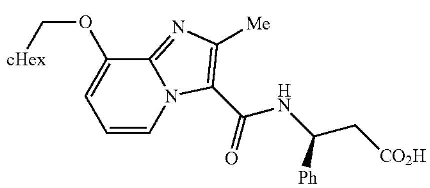
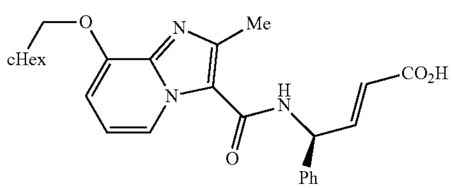
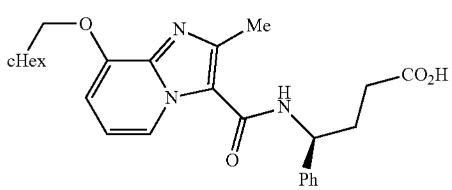
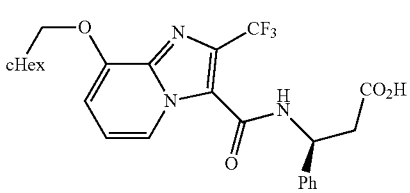
248	
249	
250	
251	
252	
253	
254	

TABLE 50

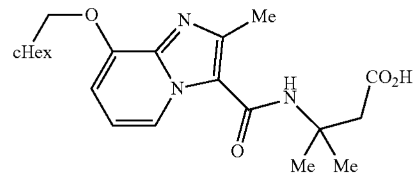
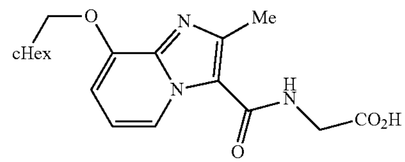
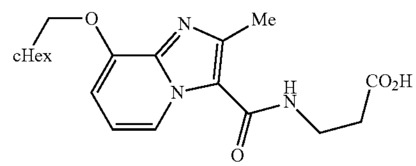
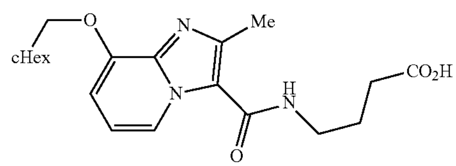
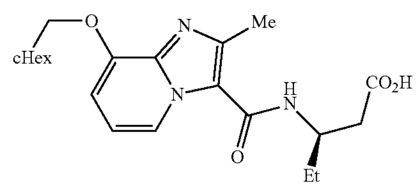
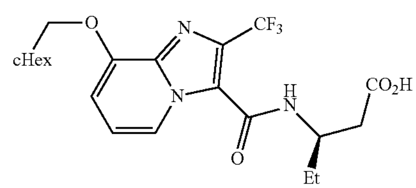
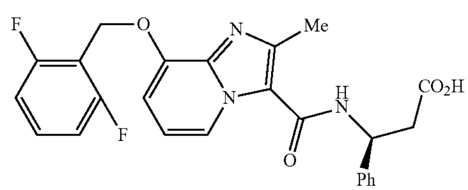
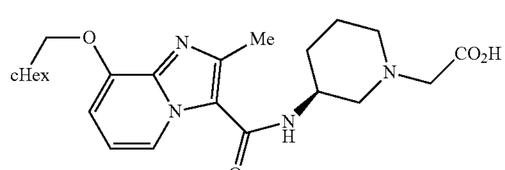
Ex	Str
255	
256	
257	
258	
259	
260	
261	
262	

TABLE 50-continued

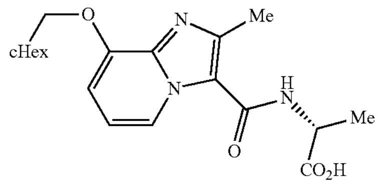
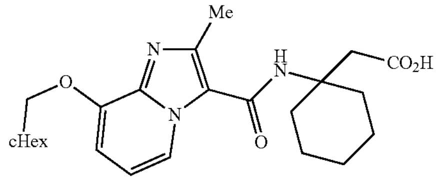
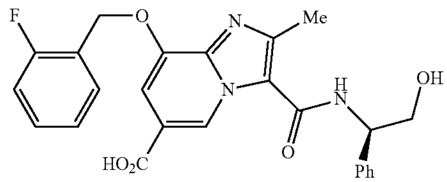
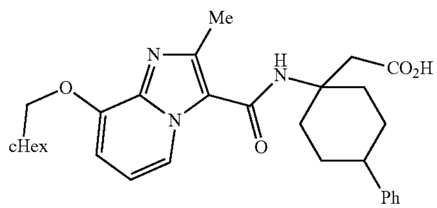
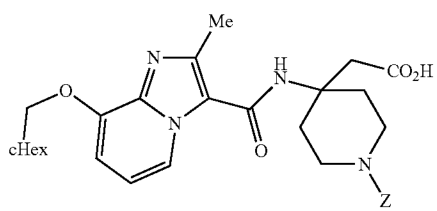
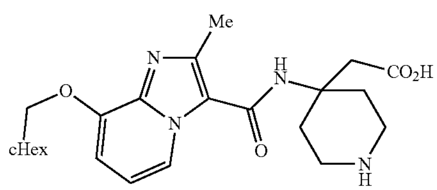
Ex	Str
263	
264	
265	
266	
267	
268	

TABLE 51

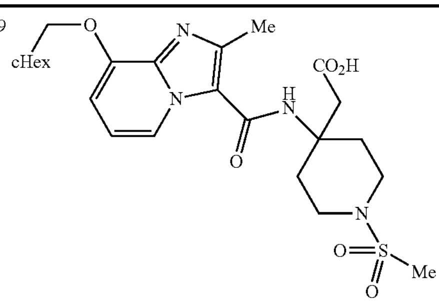
Ex	Str
269	

TABLE 51-continued

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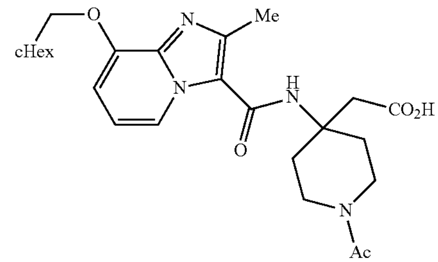
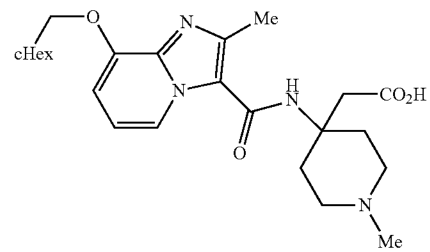
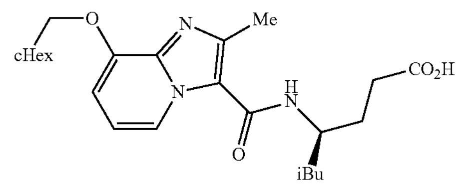
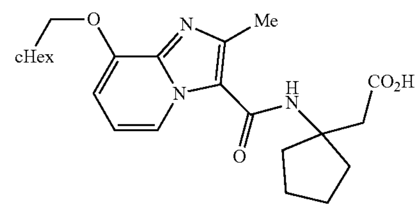
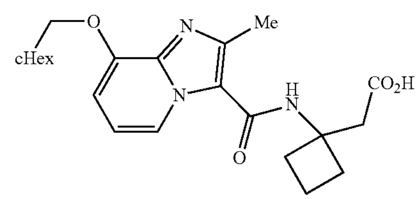
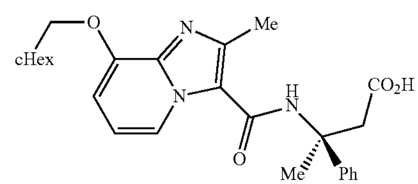
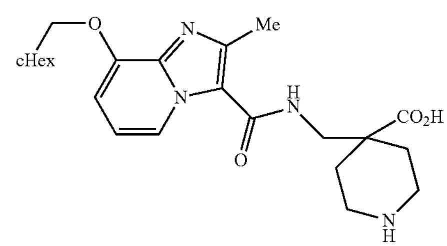
270	
271	
272	
273	
274	
275	
276	

TABLE 51-continued

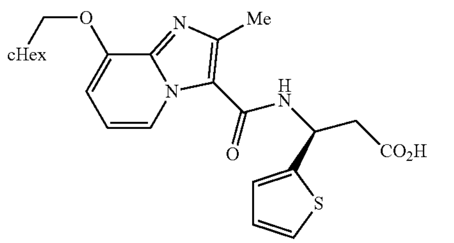
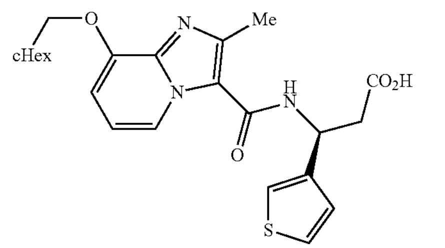
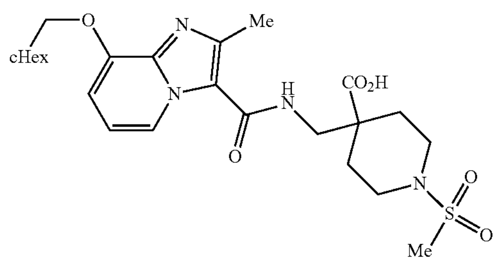
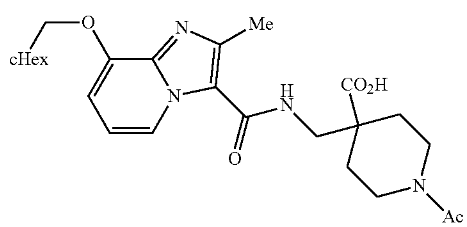
Ex	Str
277	
278	
279	
280	

TABLE 52

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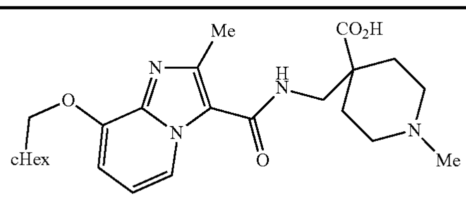
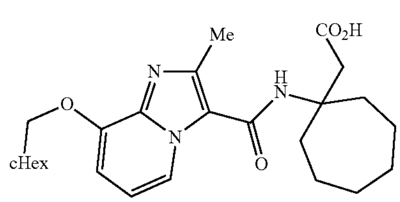
281	
282	

TABLE 52-continued

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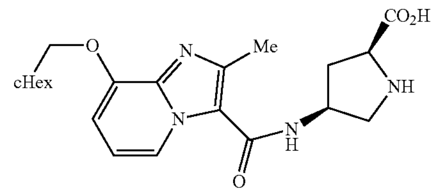
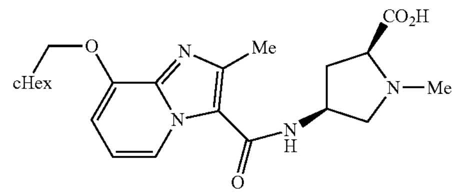
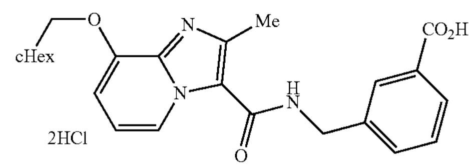
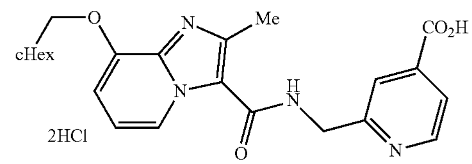
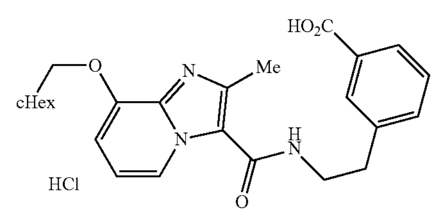
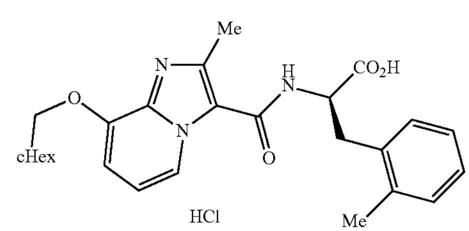
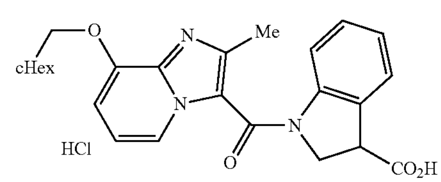
283	
284	
285	
286	
287	
288	
289	

TABLE 52-continued

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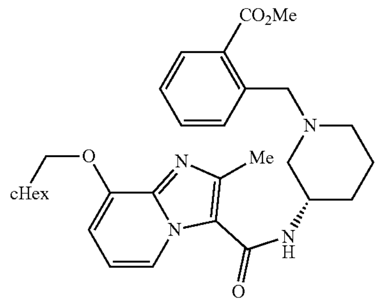
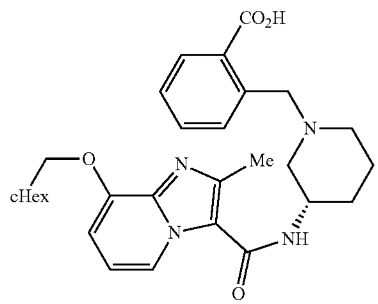
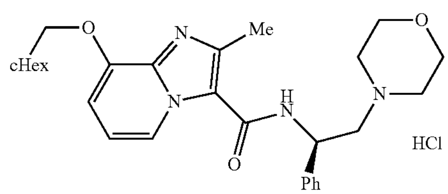
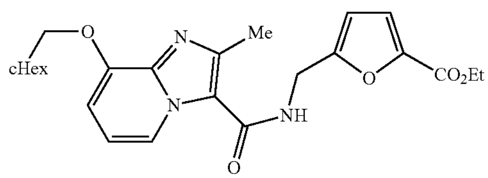
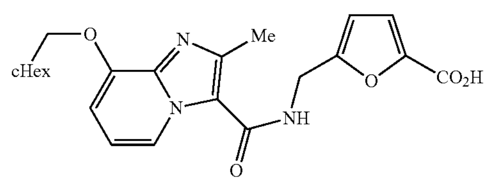
290	
291	
292	
293	
294	

TABLE 53

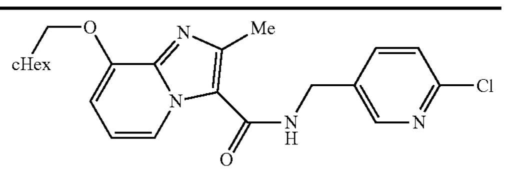
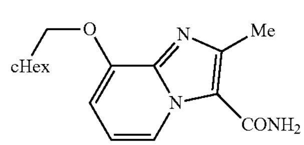
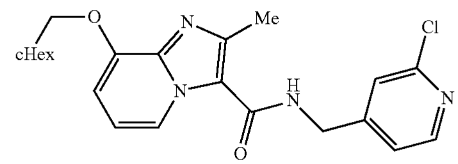
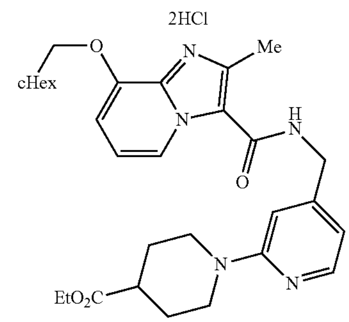
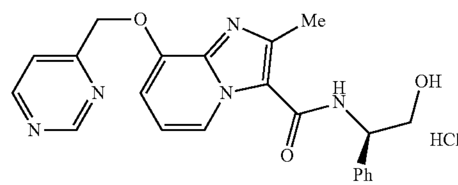
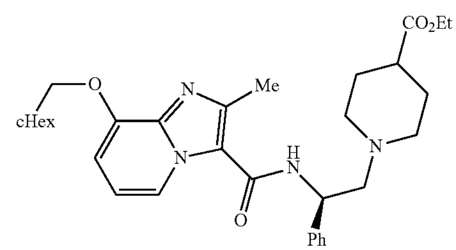
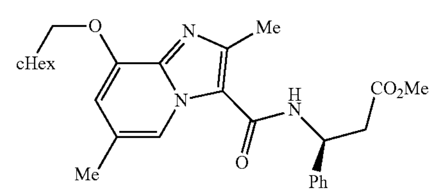
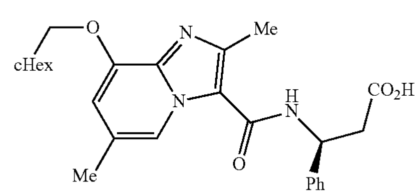
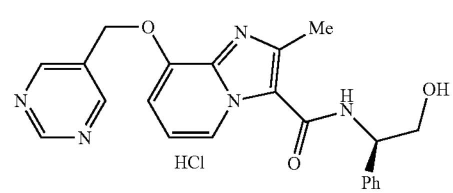
Ex	Str
295	
296	
297	
298	
299	
300	
301	
302	
303	

TABLE 53-continued

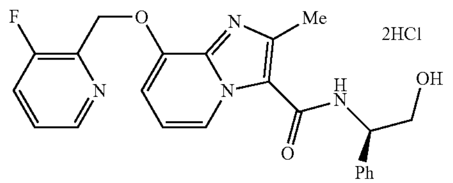
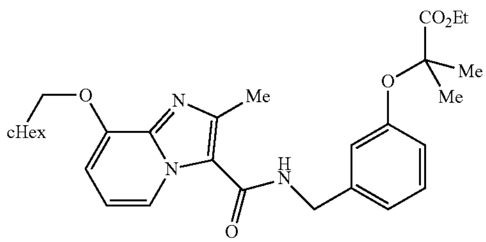
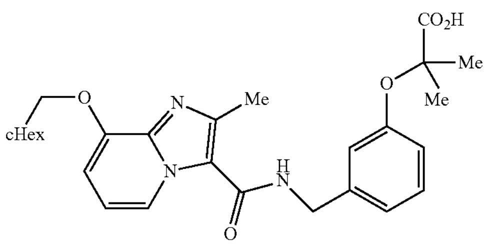
Ex	Str
304	
305	
306	

TABLE 54

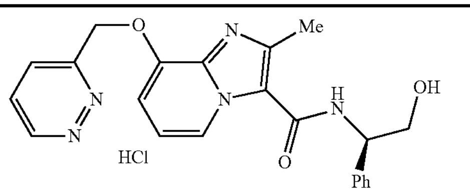
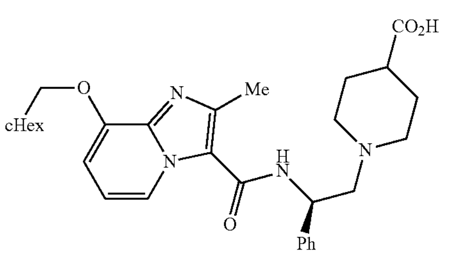
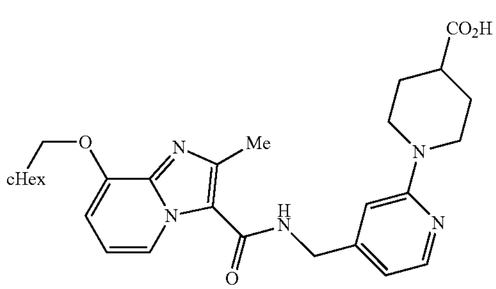
Ex	Str
307	
308	
309	

TABLE 54-continued

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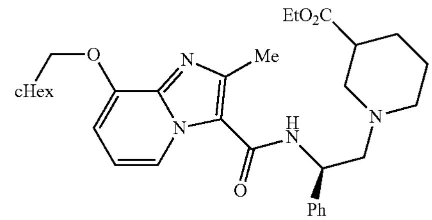
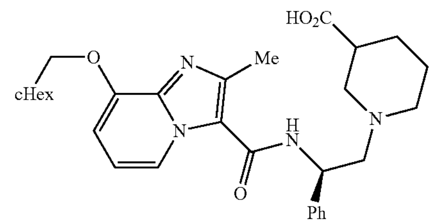
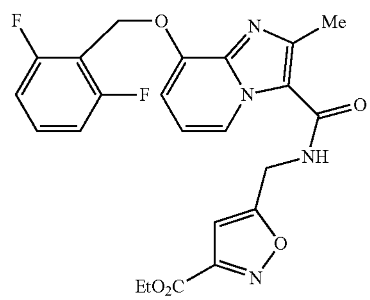
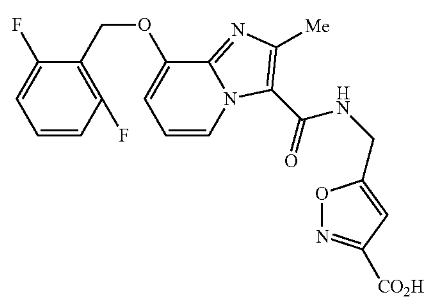
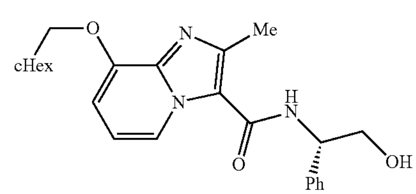
310	
311	
312	
313	
314	

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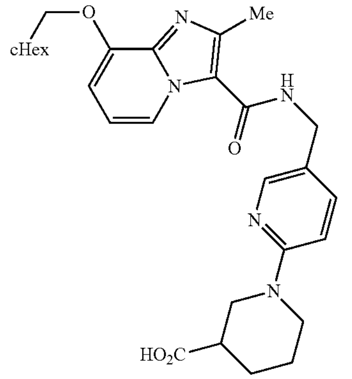
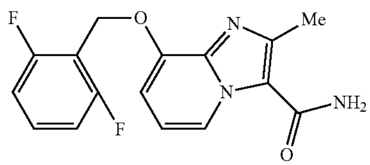
315	
316	

TABLE 55

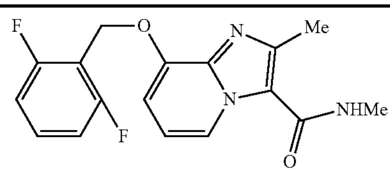
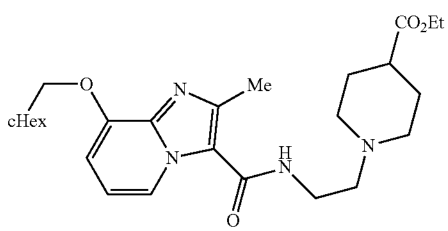
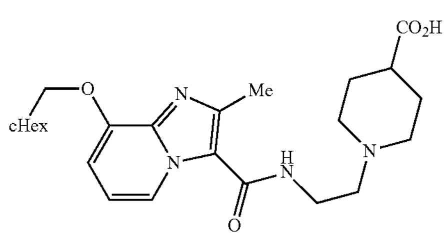
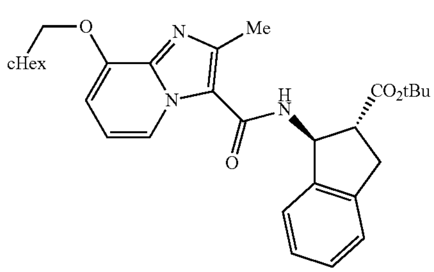
Ex	Str
317	
318	
319	
320	

TABLE 55-continued

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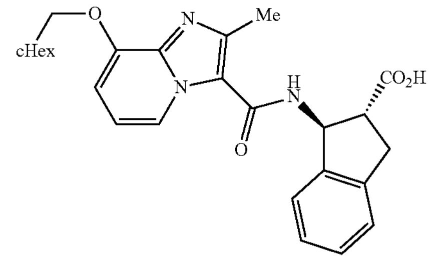
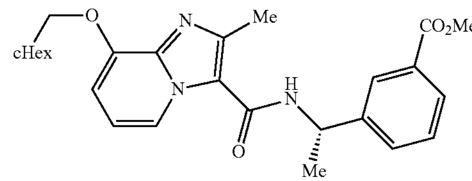
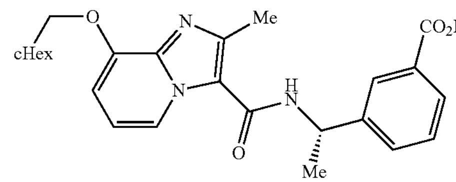
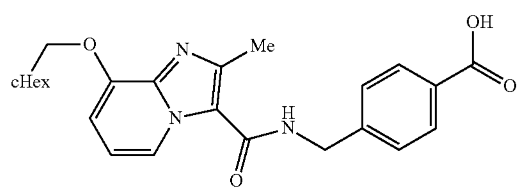
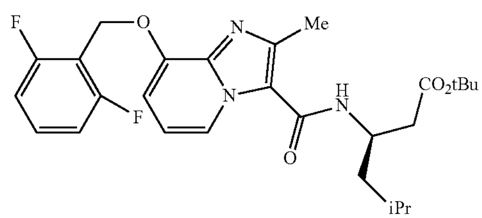
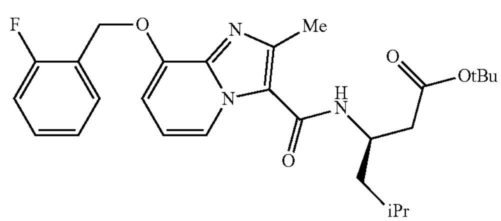
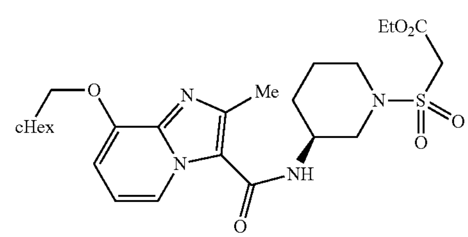
321	
322	
323	
324	
325	
326	
327	

TABLE 55-continued

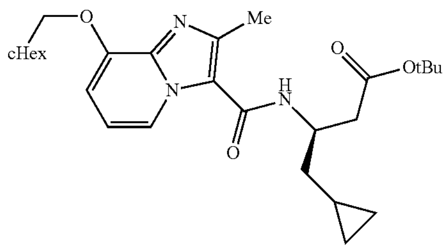
Ex	Str
328	

TABLE 56

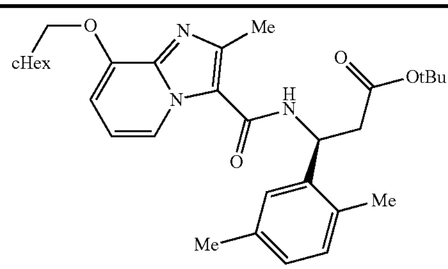
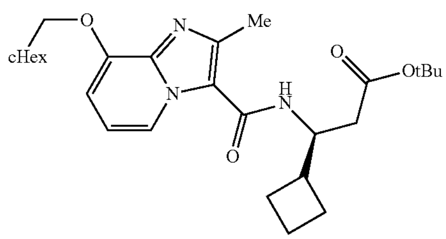
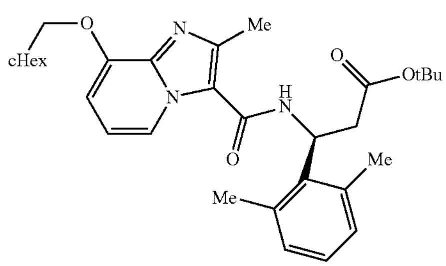
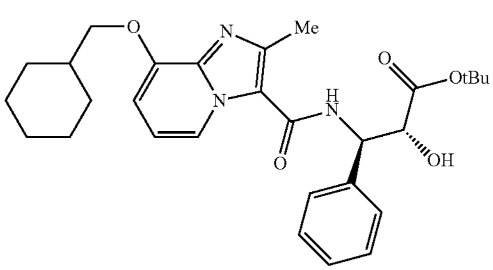
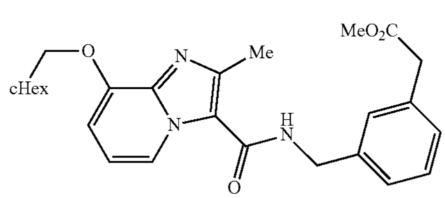
Ex	Str
329	
330	
331	
332	
333	

TABLE 56-continued

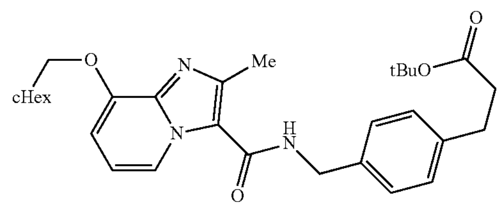
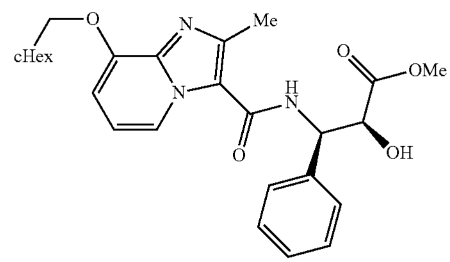
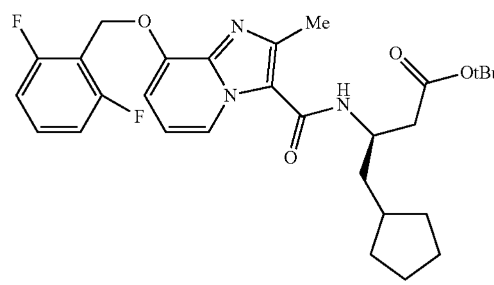
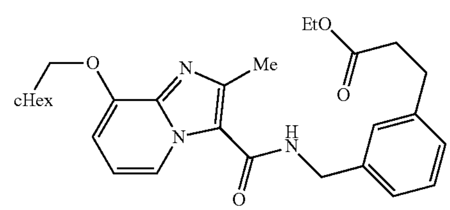
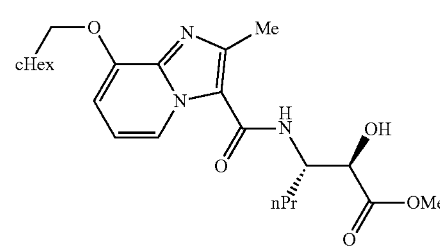
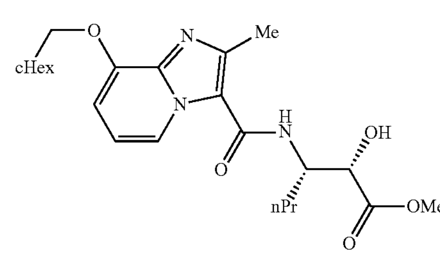
Ex	Str
334	
335	
336	
337	
338	
339	

TABLE 56-continued

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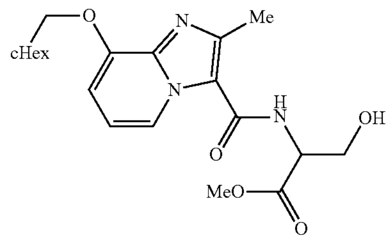
340	

TABLE 57

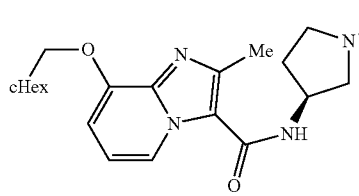
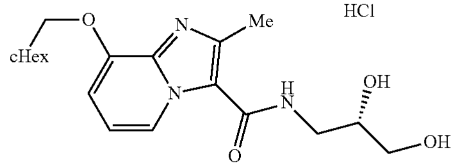
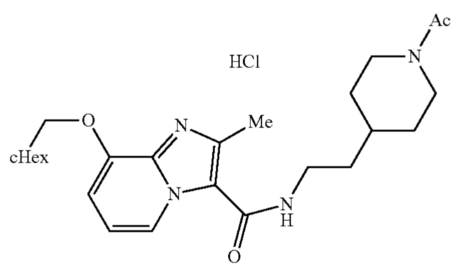
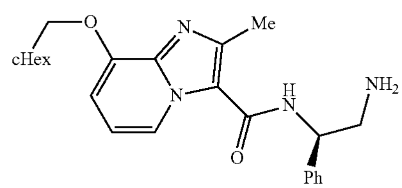
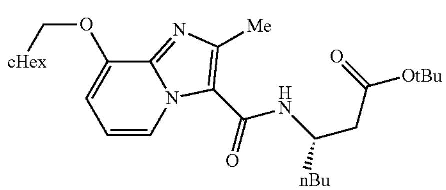
Ex	Str
341	 2HCl
342	 HCl
343	 HCl
344	
345	

TABLE 57-continued

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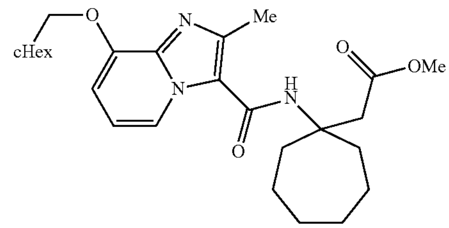
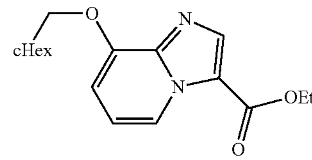
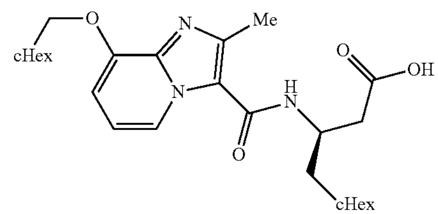
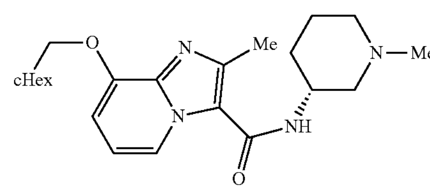
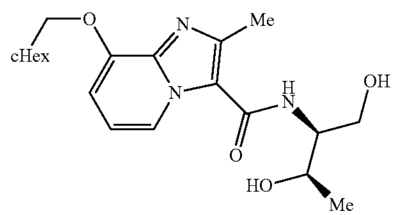
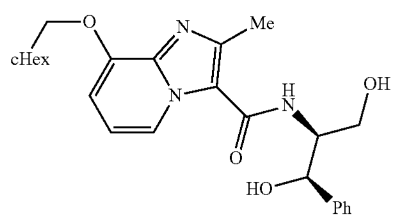
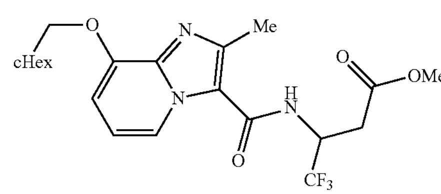
346	
347	
348	
349	
350	
351	
352	

TABLE 57-continued

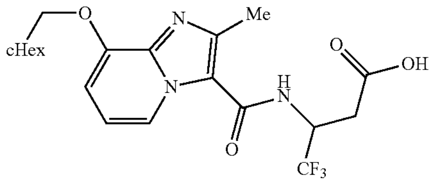
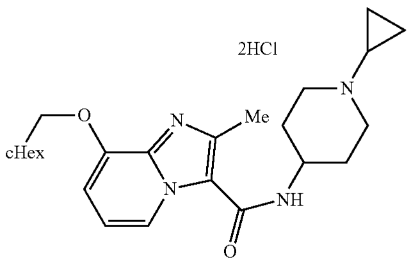
Ex	Str
353	
354	2HCl 

TABLE 58

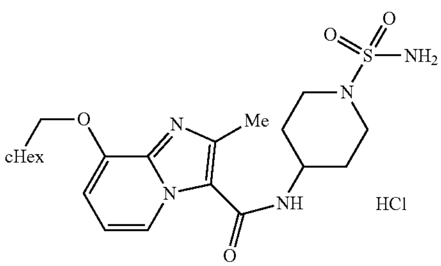
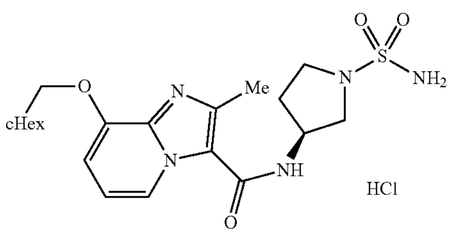
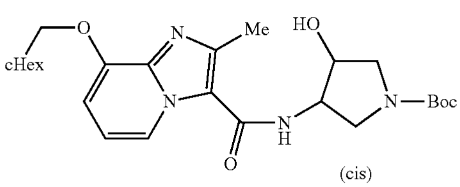
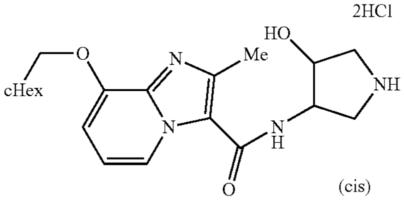
Ex	Str
355	 HCl
356	 HCl
357	 (cis)
358	2HCl  (cis)

TABLE 58-continued

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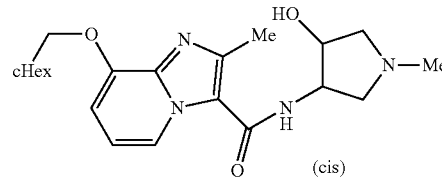
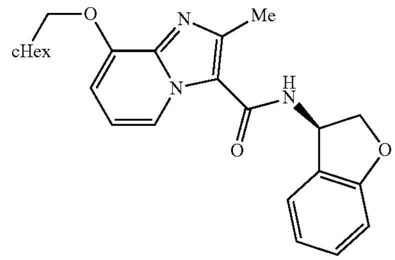
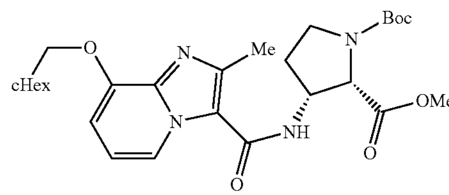
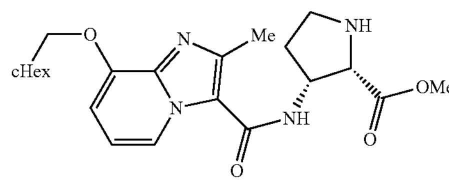
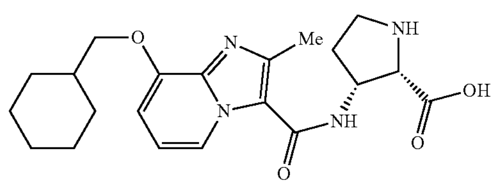
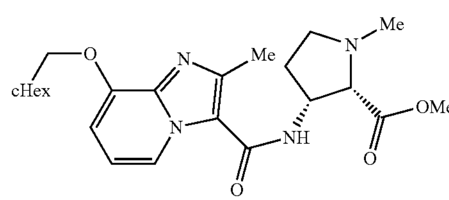
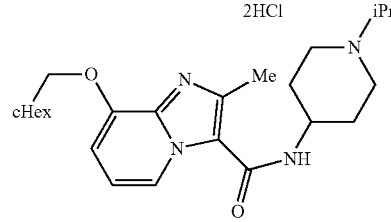
359	2HCl  (cis)
360	
361	
362	 2HCl
363	
364	
365	2HCl 

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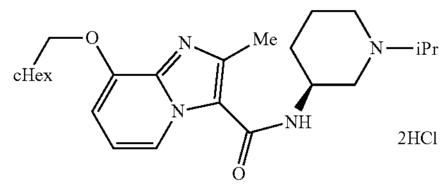
366	

TABLE 59

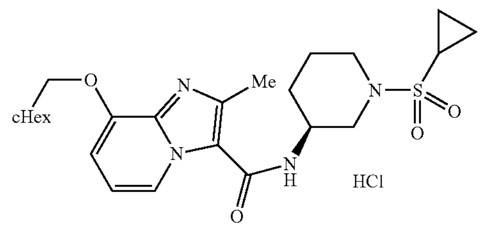
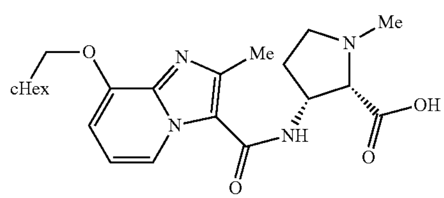
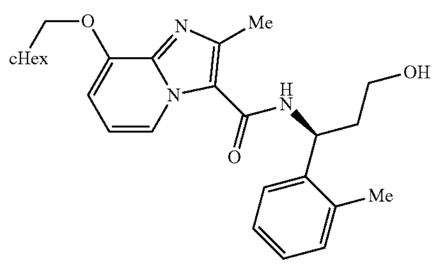
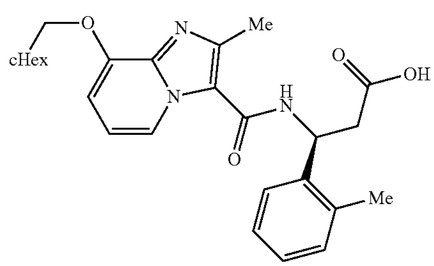
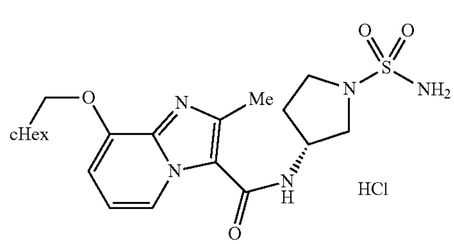
Ex	Str
367	
368	
369	
370	
371	

TABLE 59-continued

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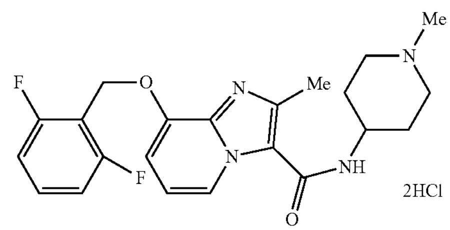
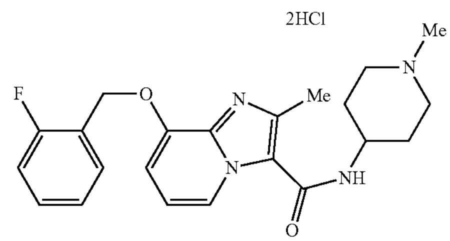
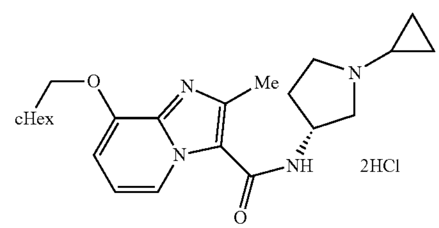
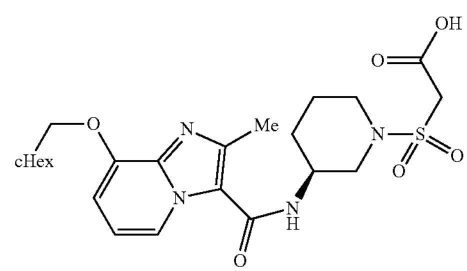
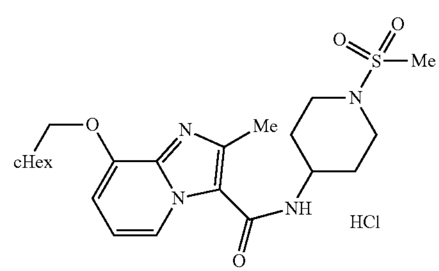
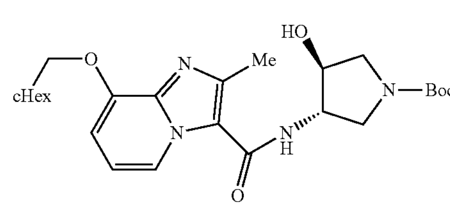
372	
373	
374	
375	
376	
377	

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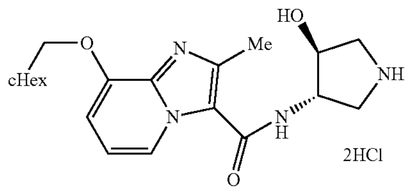
Ex	Str
378	

TABLE 60

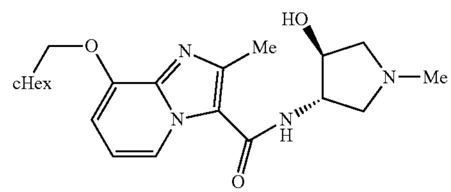
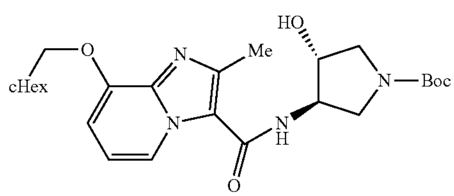
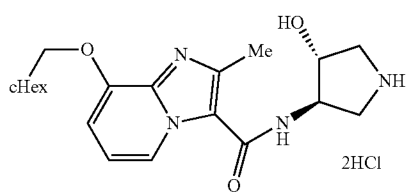
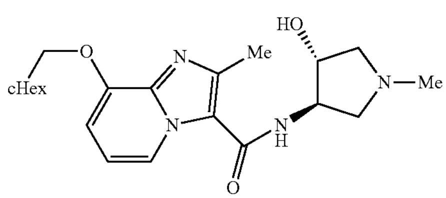
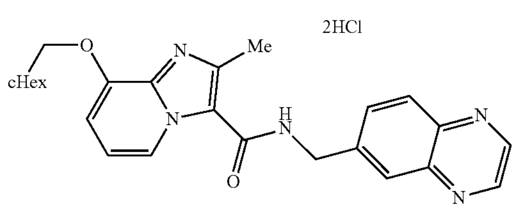
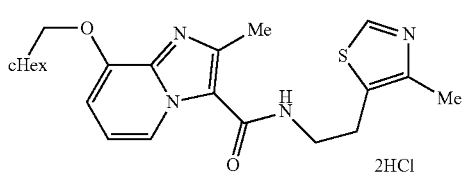
Ex	Str
379	
380	
381	
382	
383	
384	

TABLE 60-continued

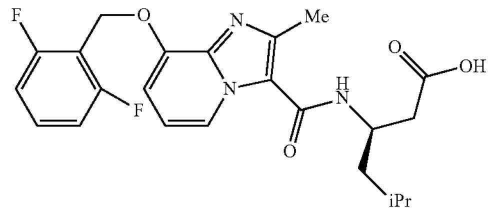
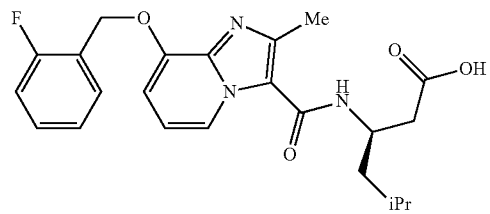
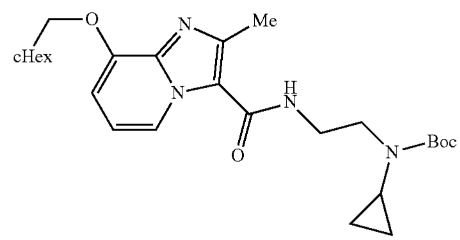
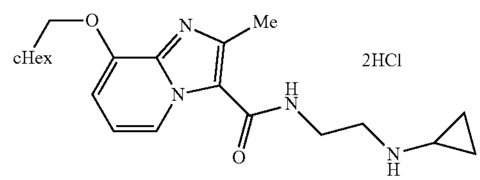
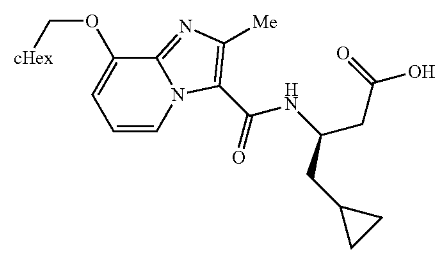
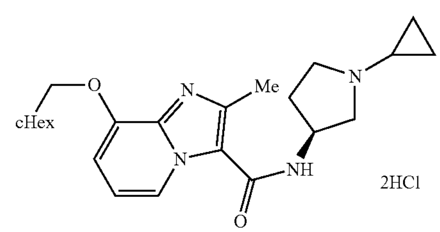
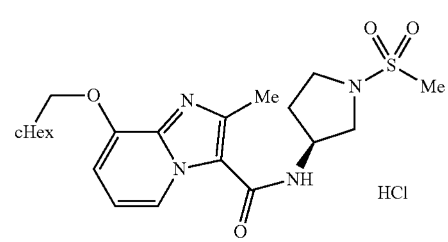
Ex	Str
385	
386	
387	
388	
389	
390	
391	

TABLE 60-continued

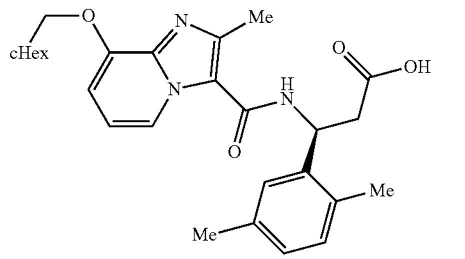
Ex	Str
392	

TABLE 61

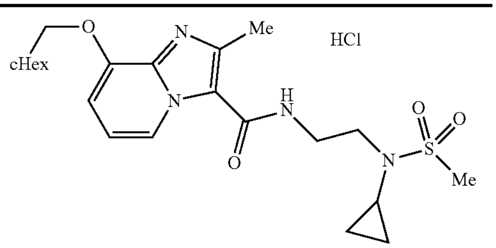
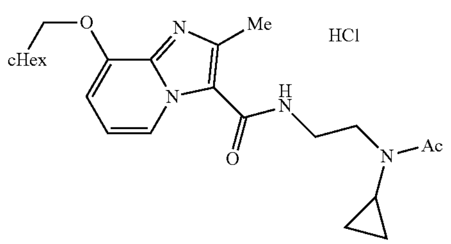
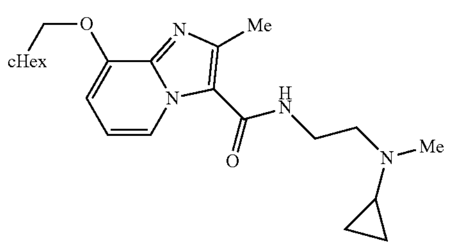
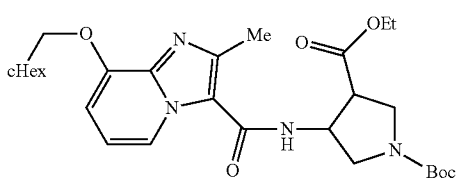
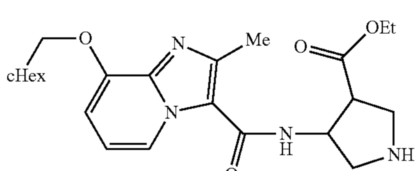
Ex	Str
393	 HCl
394	 HCl
395	
396	 (trans)
397	 2HCl (trans)

TABLE 61-continued

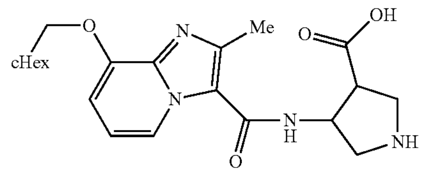
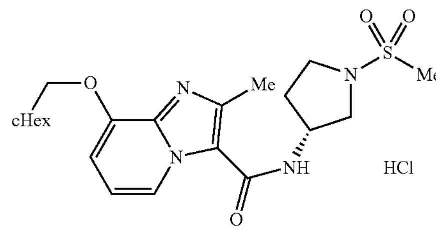
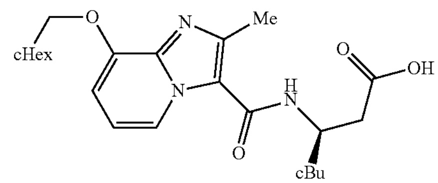
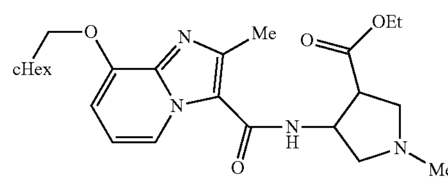
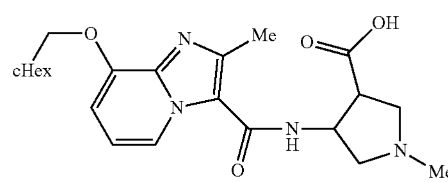
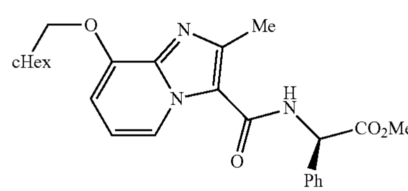
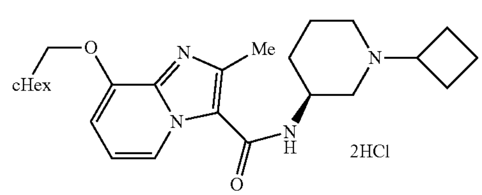
Ex	Str
398	 (trans)
399	 HCl
400	
401	 (trans)
402	 (trans)
403	
404	 2HCl

TABLE 62

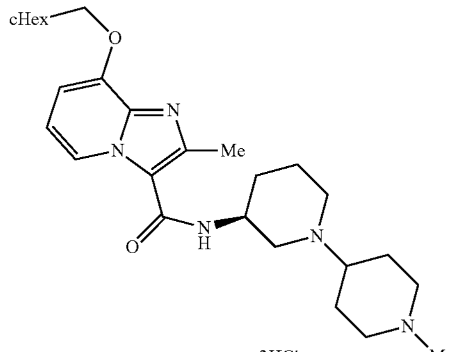
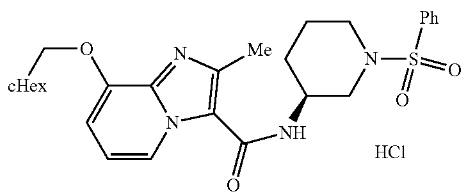
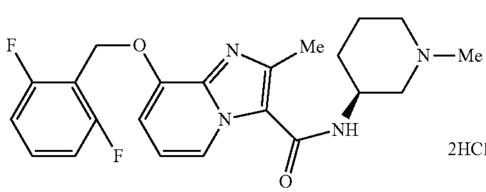
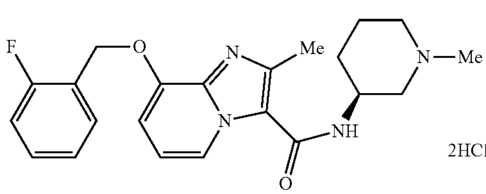
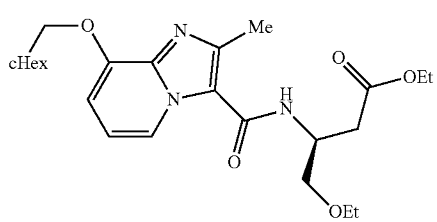
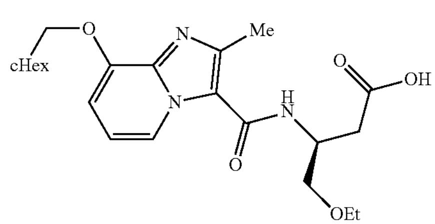
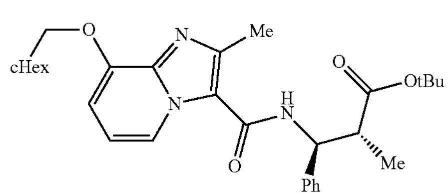
Ex	Str
405	 3HCl
406	 HCl
407	 2HCl
408	 2HCl
409	
410	
411	

TABLE 62-continued

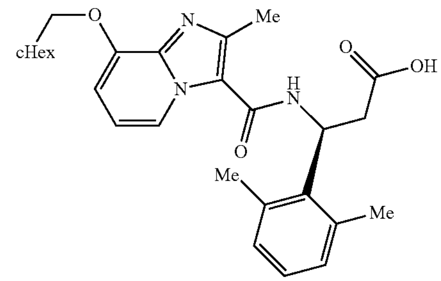
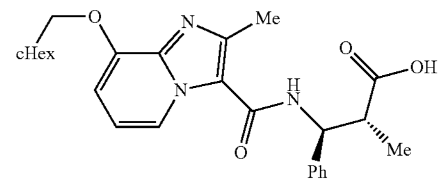
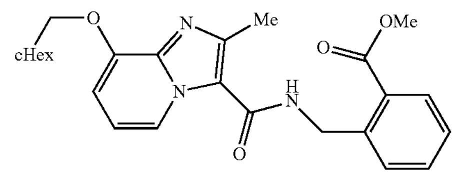
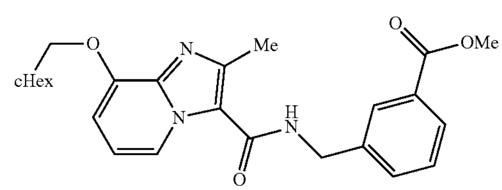
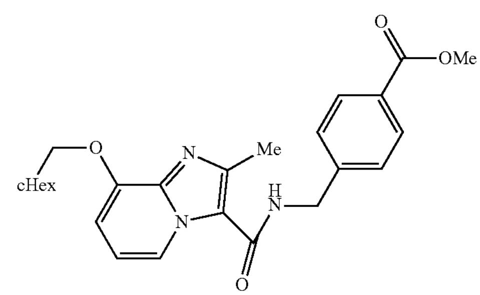
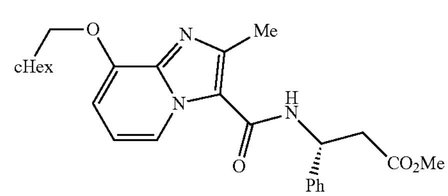
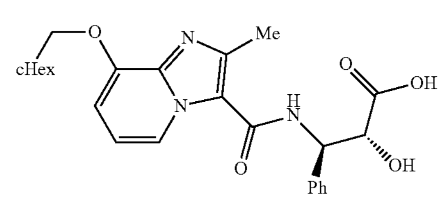
Ex	Str
412	
413	
414	
415	
416	
417	
418	

TABLE 63

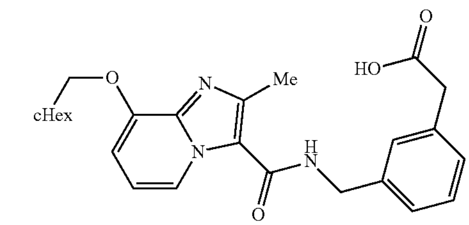
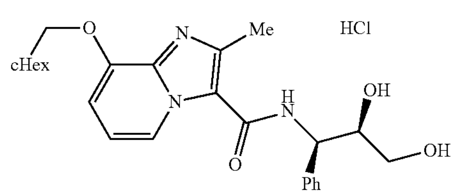
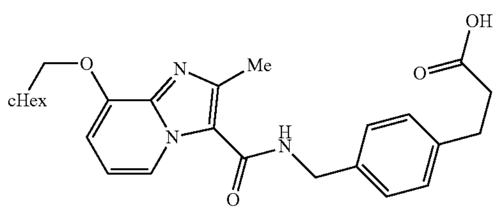
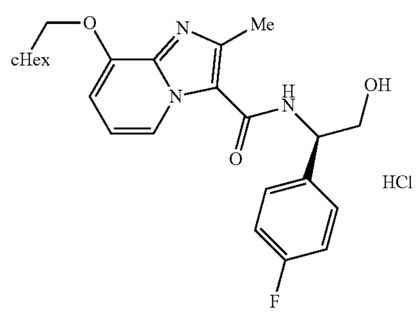
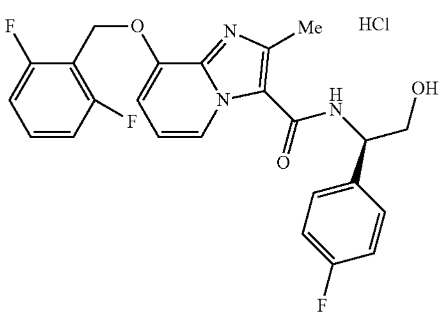
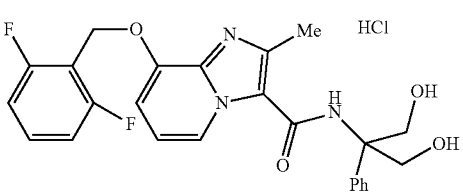
Ex	Str
419	
420	 HCl
421	
422	 HCl
423	 HCl
424	 HCl

TABLE 63-continued

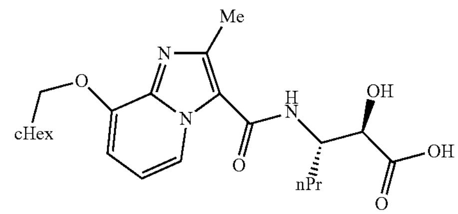
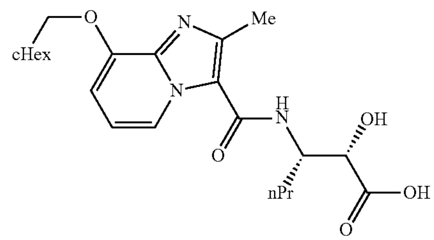
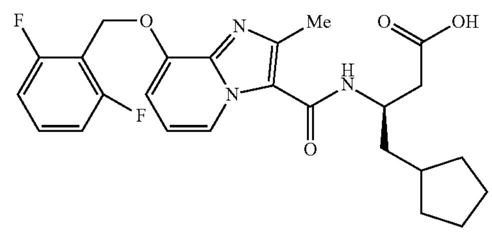
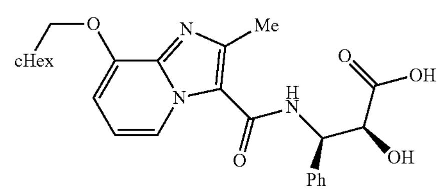
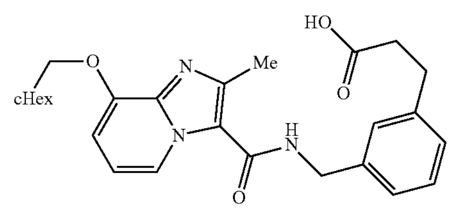
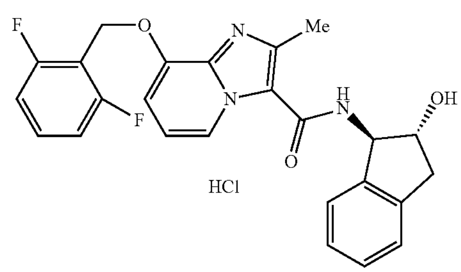
Ex	Str
425	
426	
427	
428	
429	
430	 HCl

TABLE 64

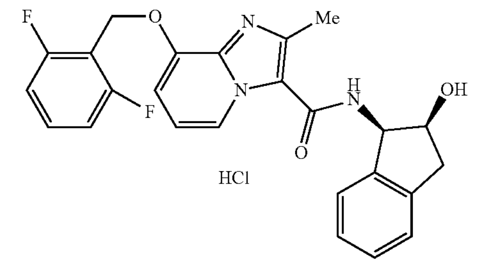
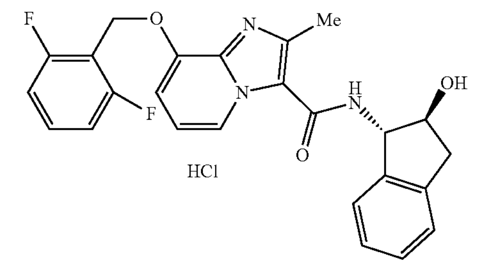
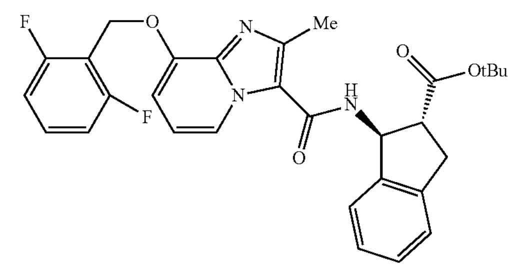
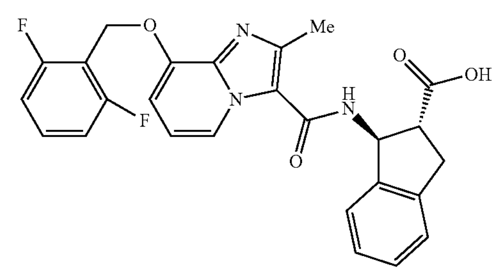
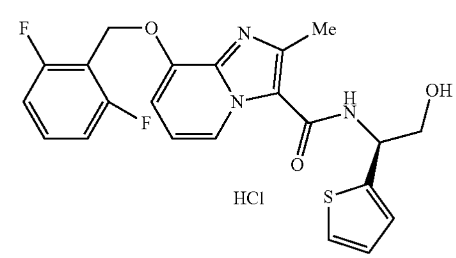
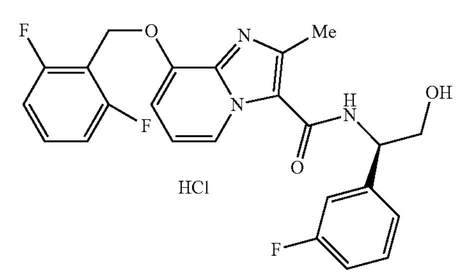
Ex	Str
431	 HCl
432	 HCl
433	
434	
435	 HCl
436	 HCl

TABLE 64-continued

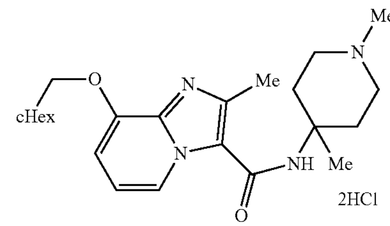
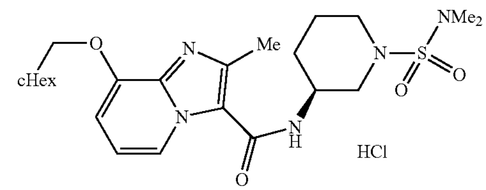
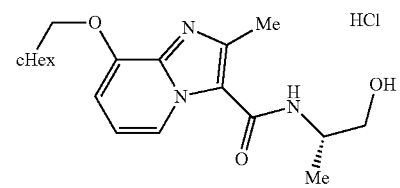
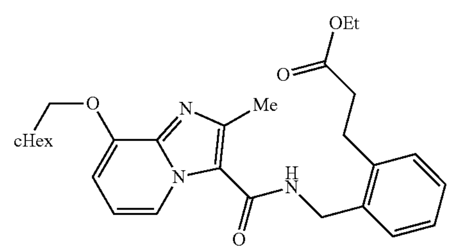
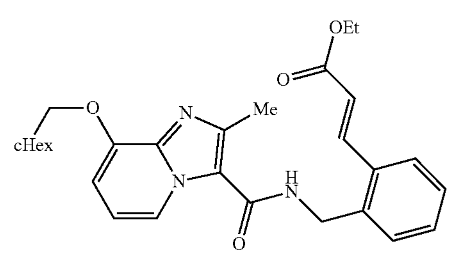
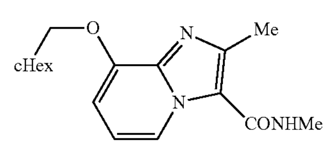
Ex	Str
437	 2HCl
438	 HCl
439	 HCl
440	
441	
442	

TABLE 65

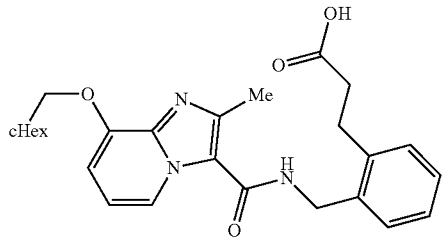
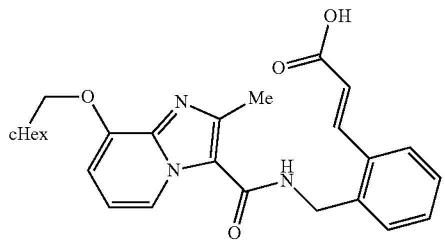
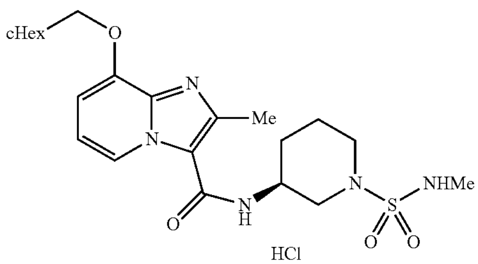
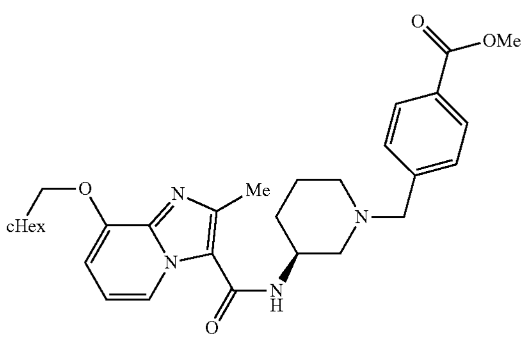
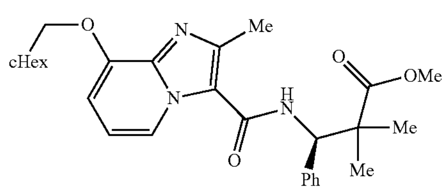
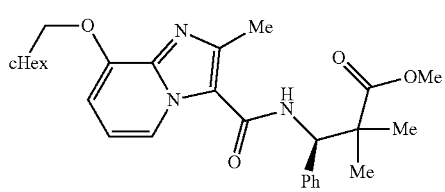
Ex	Str
443	
444	
445	
446	
447	
448	

TABLE 65-continued

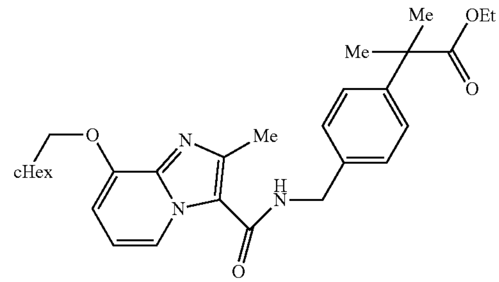
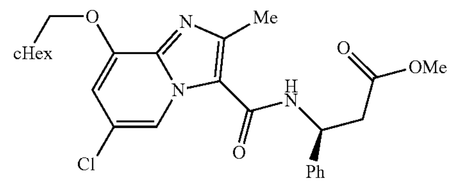
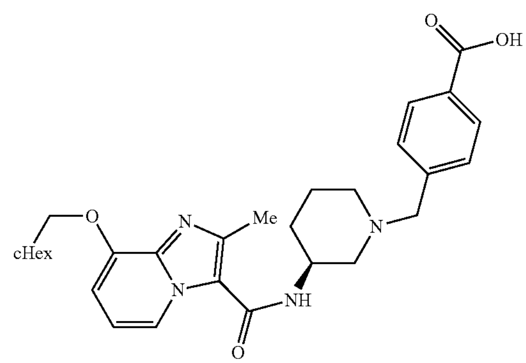
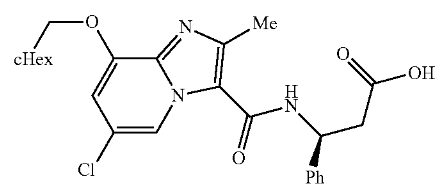
Ex	Str
449	
450	
451	
452	

TABLE 66

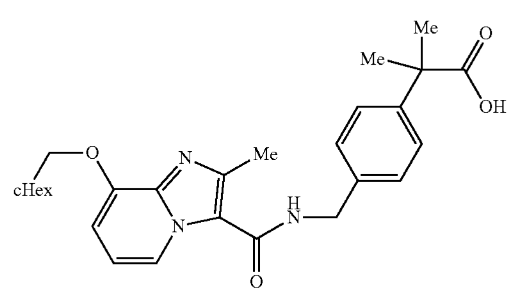
Ex	Str
453	

TABLE 66-continued

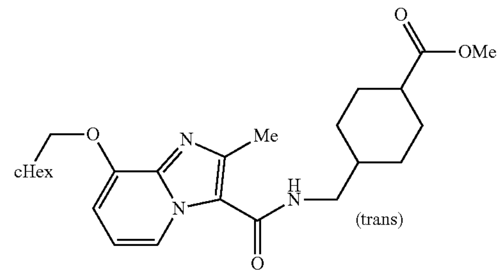
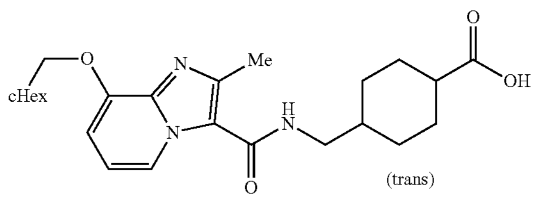
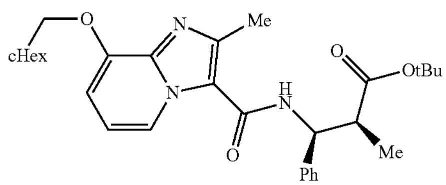
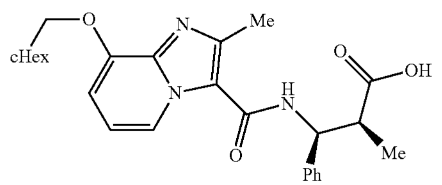
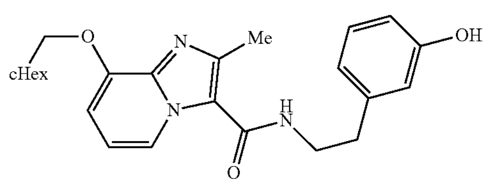
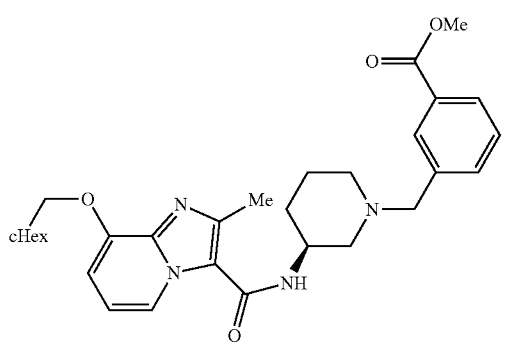
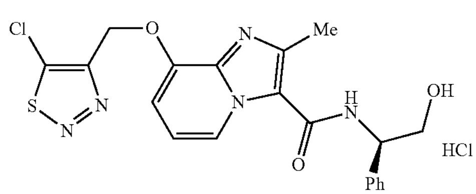
Ex	Str
454	
455	
456	
457	
458	
459	
460	

TABLE 66-continued

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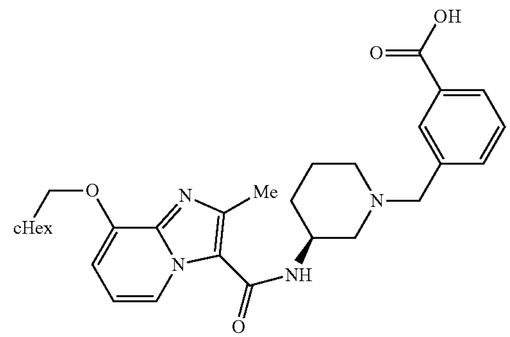
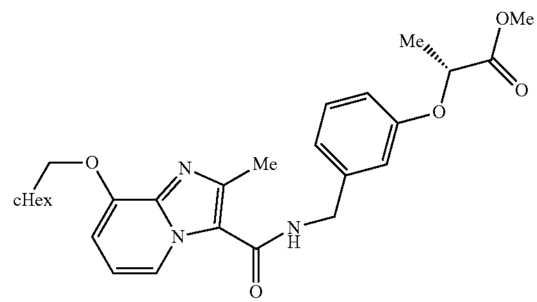
461	
462	

TABLE 67

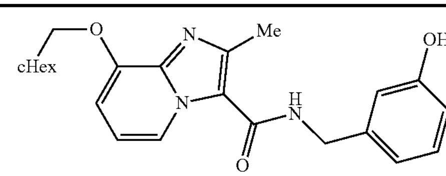
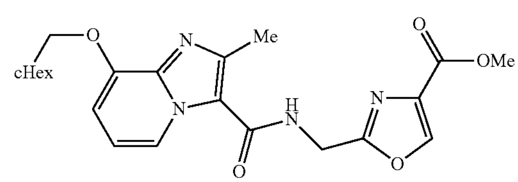
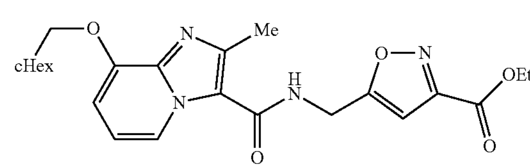
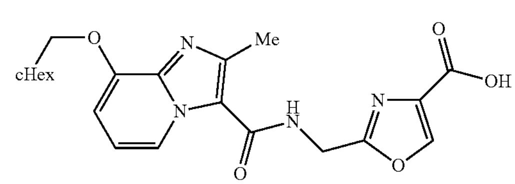
Ex	Str
463	
464	
465	
466	

TABLE 67-continued

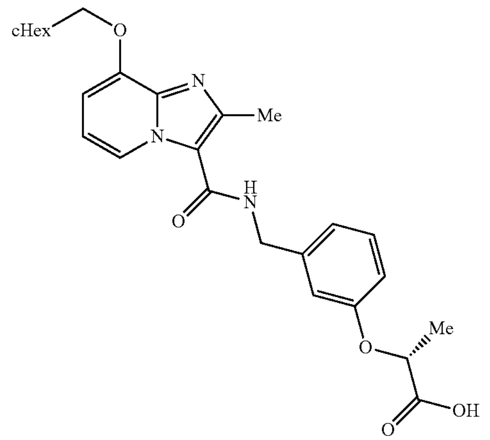
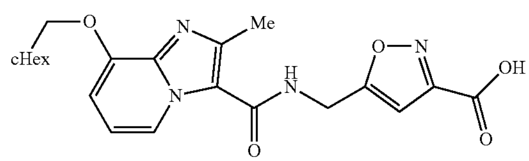
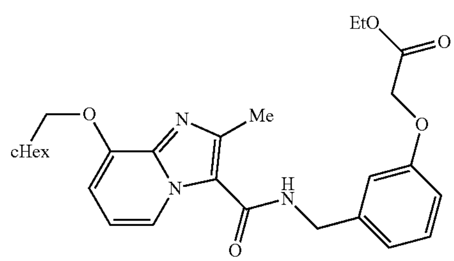
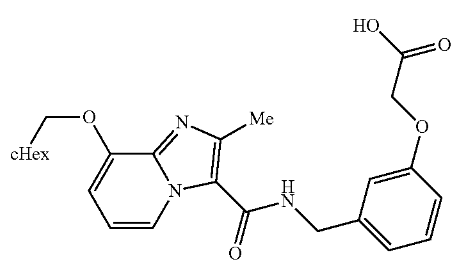
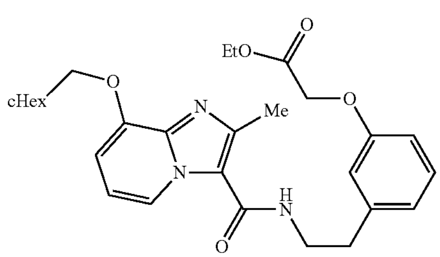
Ex	Str
467	
468	
469	
470	
471	

TABLE 67-continued

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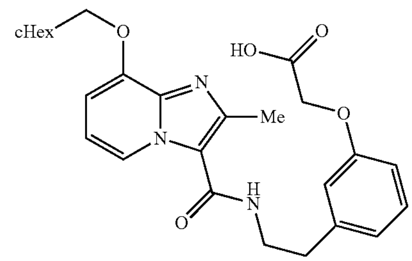
472	

TABLE 68

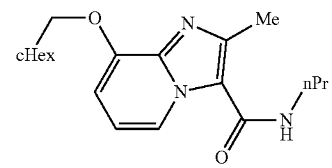
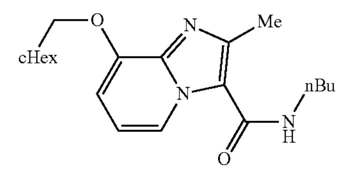
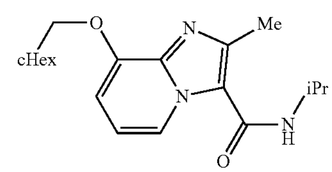
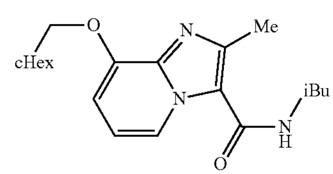
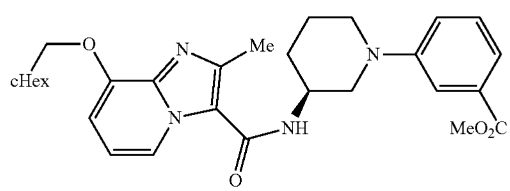
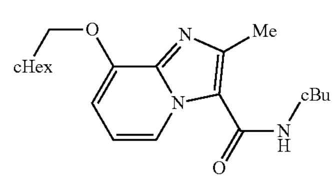
Ex	Str
473	
474	
475	
476	
477	
478	

TABLE 68-continued

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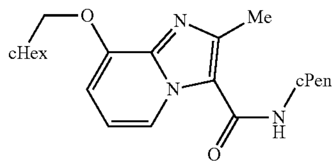
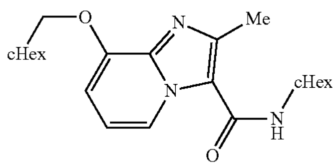
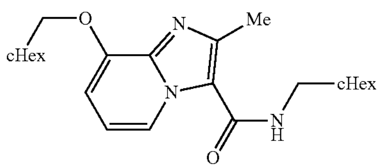
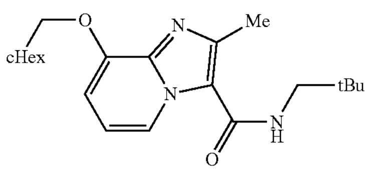
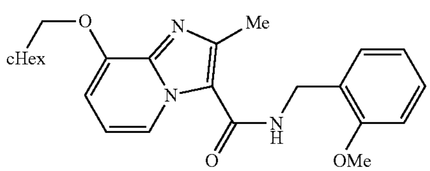
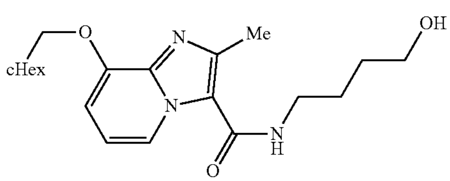
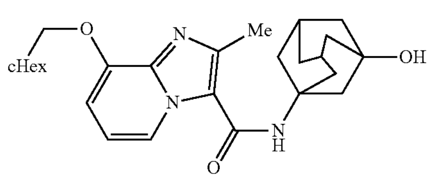
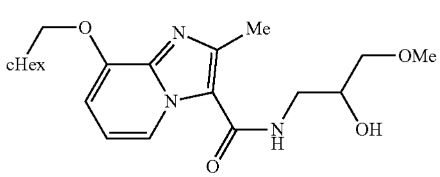
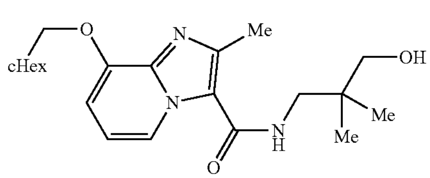
479	
480	
481	
482	
483	
484	
485	
486	
487	

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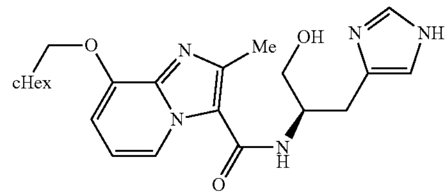
488	

TABLE 69

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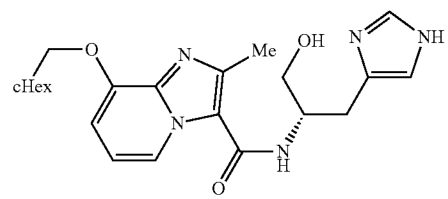
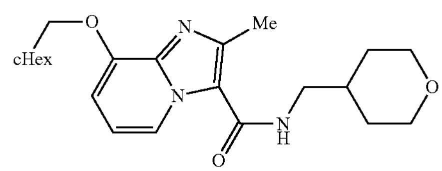
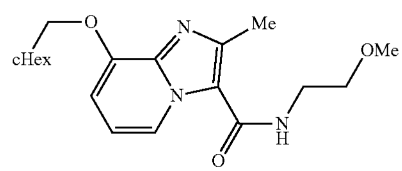
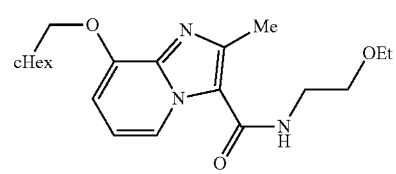
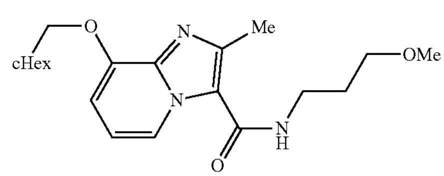
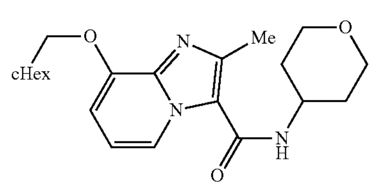
489	
490	
491	
492	
493	
494	

TABLE 69-continued

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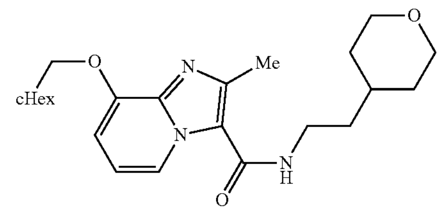
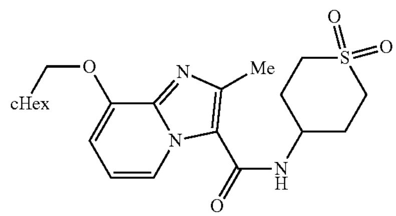
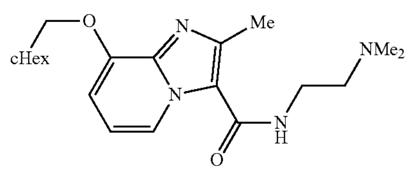
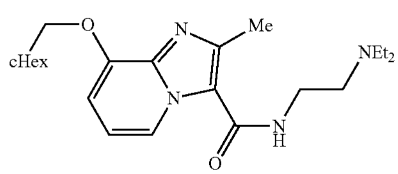
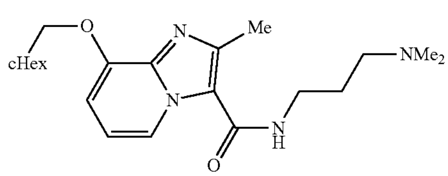
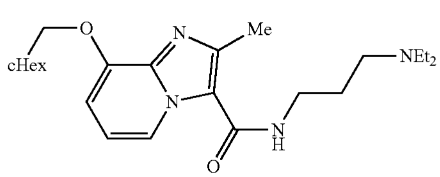
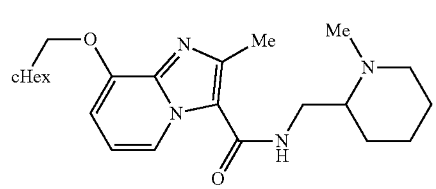
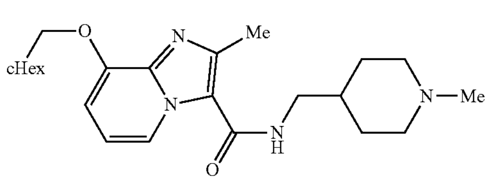
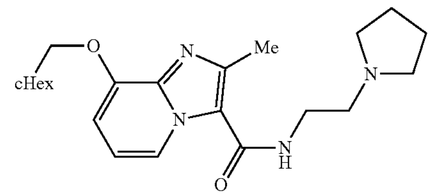
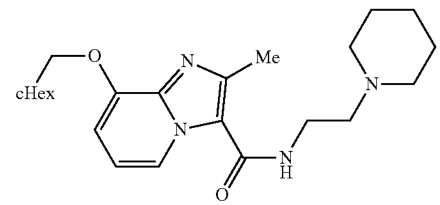
495	
496	
497	
498	
499	
500	
501	
502	
503	
504	

TABLE 70

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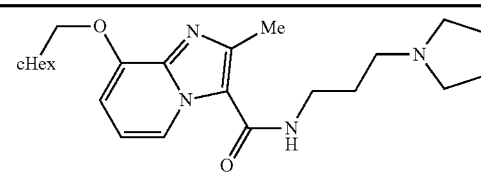
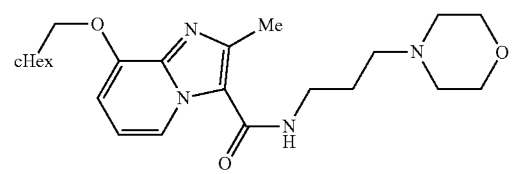
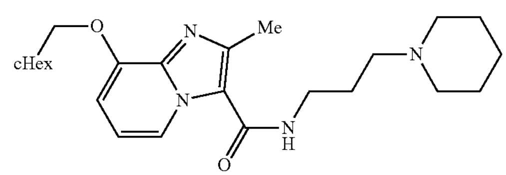
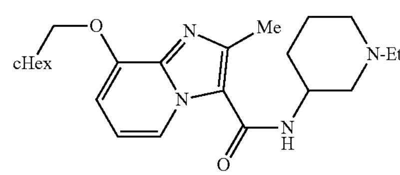
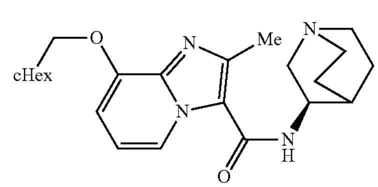
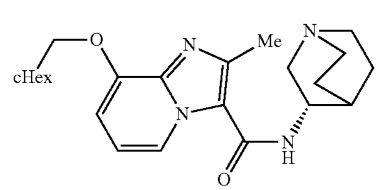
505	
506	
507	
508	
509	
510	

TABLE 70-continued

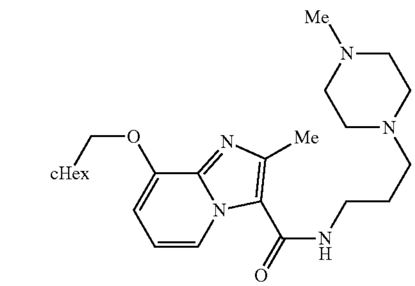
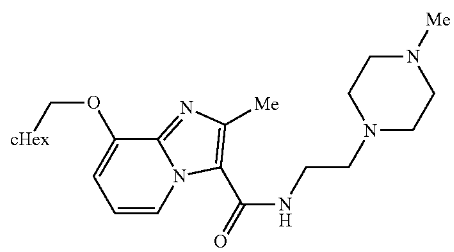
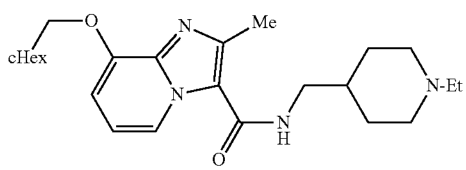
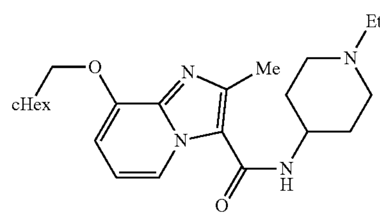
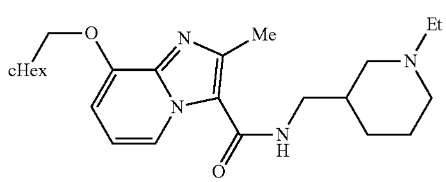
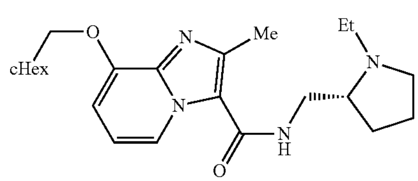
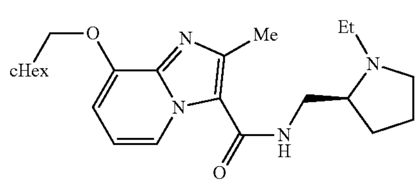
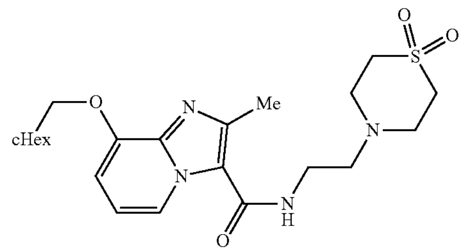
Ex	Str
511	
512	
513	
514	
515	
516	
517	
518	

TABLE 71

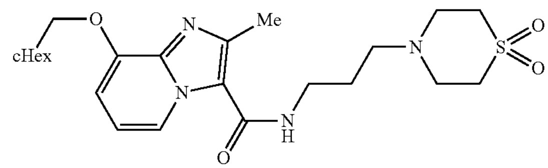
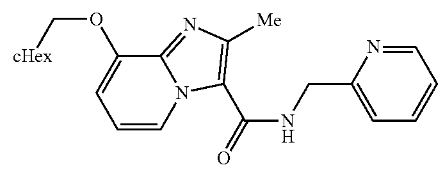
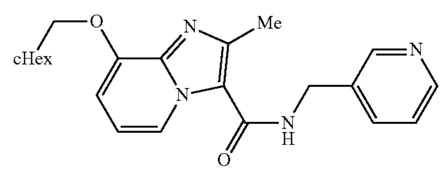
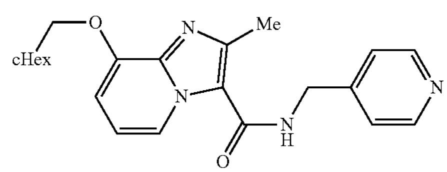
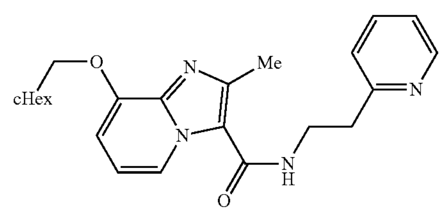
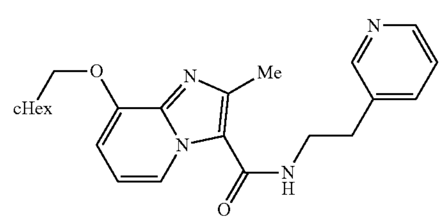
Ex	Str
519	
520	
521	
522	
523	
524	

TABLE 71-continued

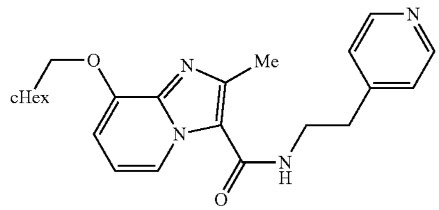
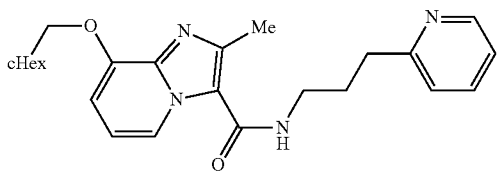
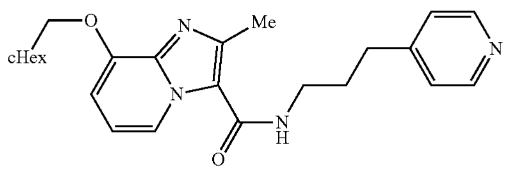
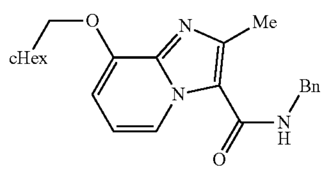
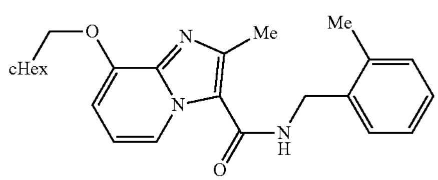
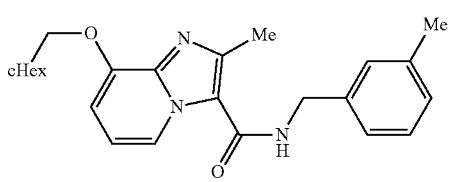
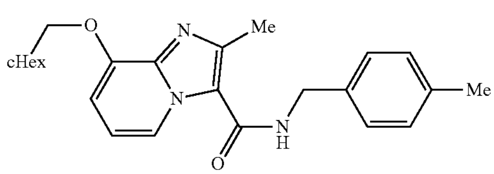
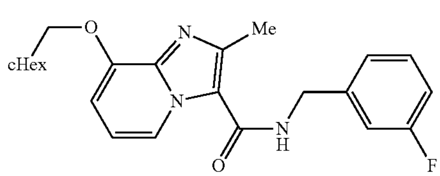
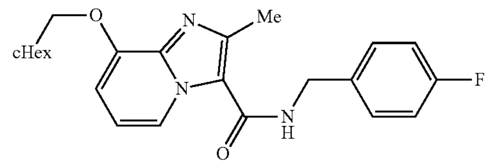
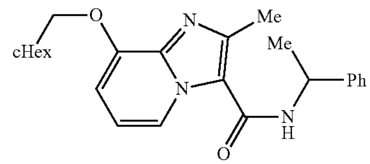
Ex	Str
525	
526	
527	
528	
529	
530	
531	
532	
533	
534	

TABLE 72

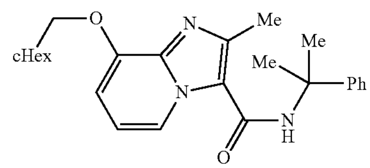
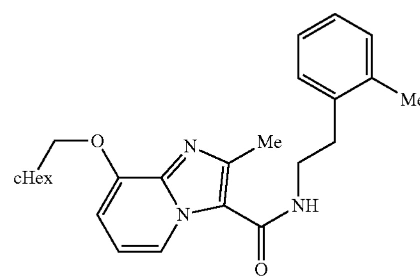
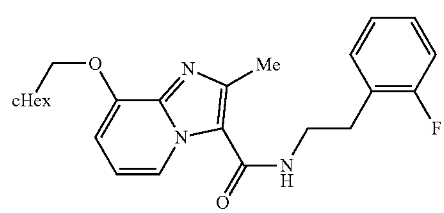
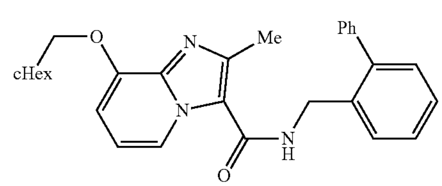
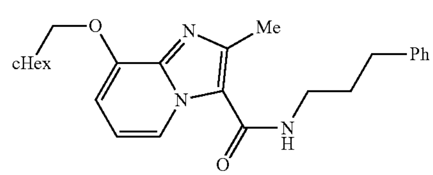
Ex	Str
535	
536	
537	
538	
539	

TABLE 72-continued

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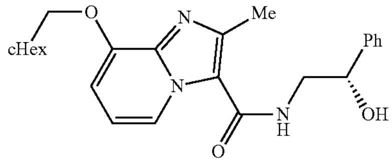
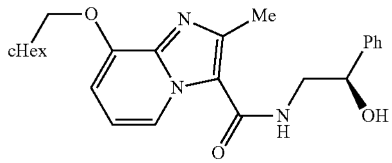
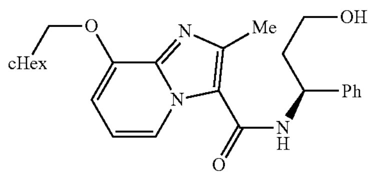
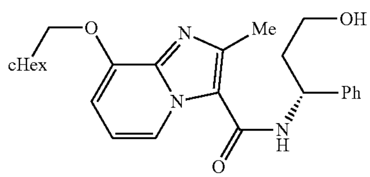
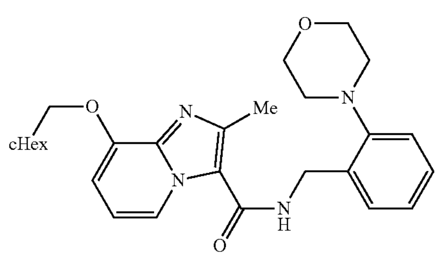
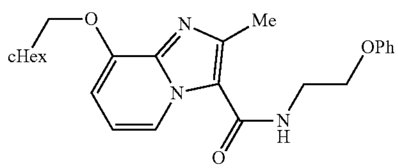
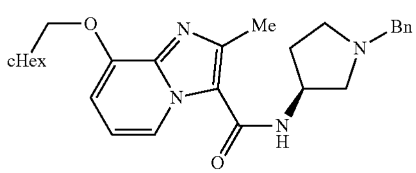
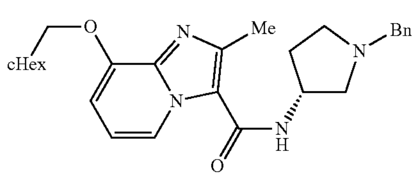
540	
541	
542	
543	
544	
545	
546	
547	

TABLE 72-continued

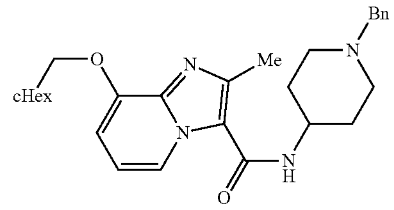
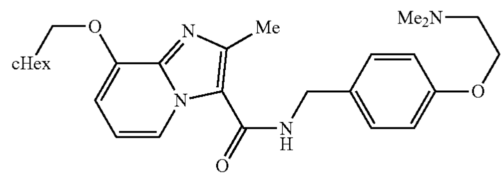
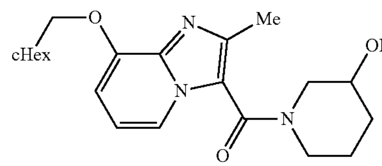
Ex	Str
548	
549	
550	

TABLE 73

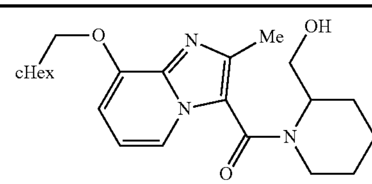
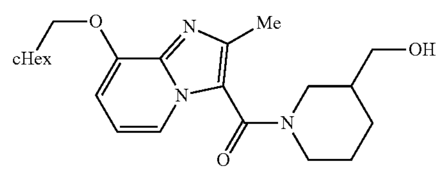
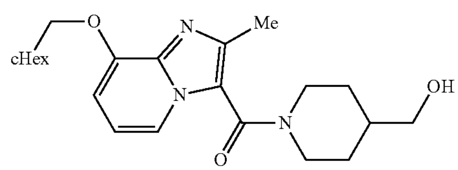
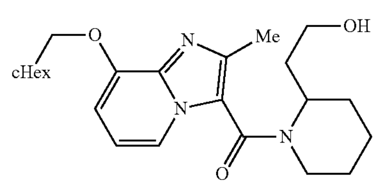
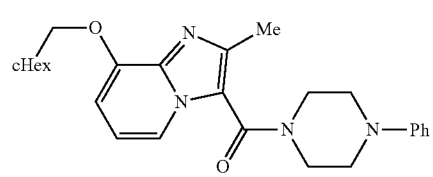
Ex	Str
551	
552	
553	
554	
555	

TABLE 73-continued

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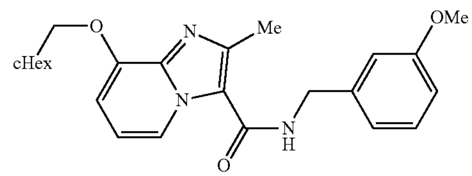
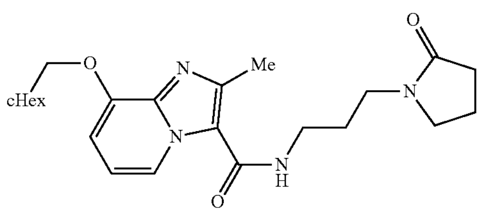
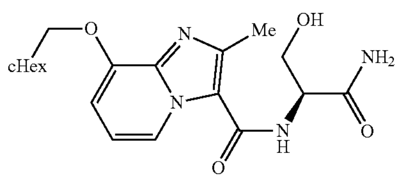
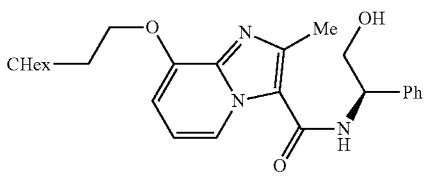
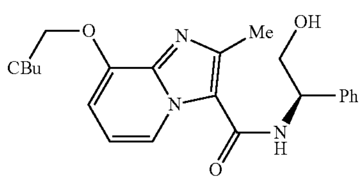
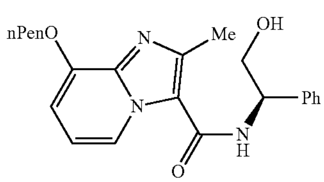
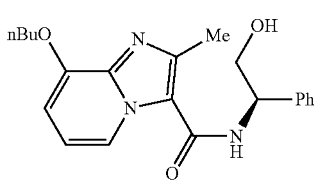
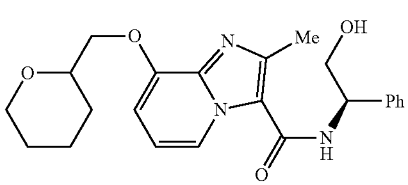
556	
557	
558	
559	
560	
561	
562	
563	

TABLE 73-continued

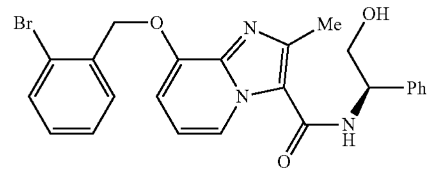
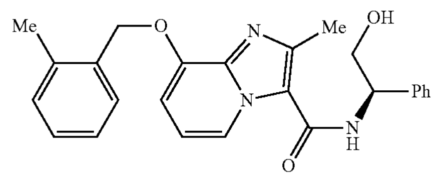
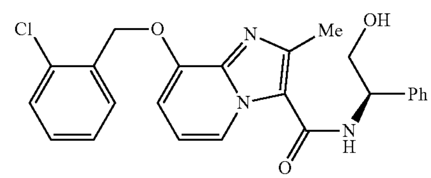
Ex	Str
564	
565	
566	

TABLE 74

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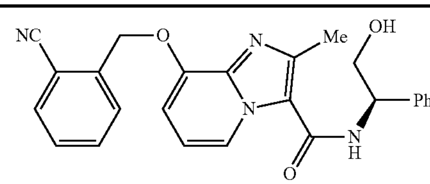
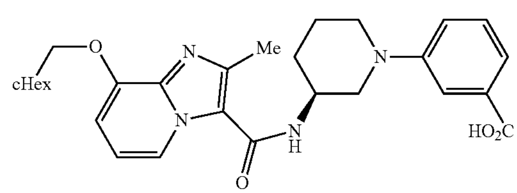
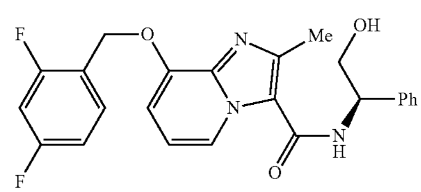
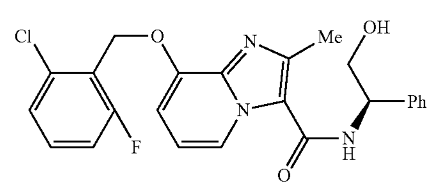
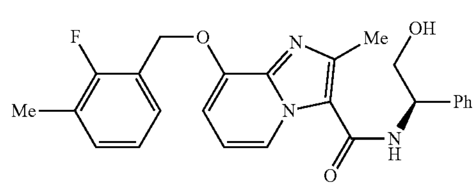
567	
568	
569	
570	
571	

TABLE 74-continued

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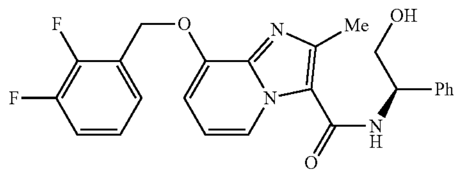
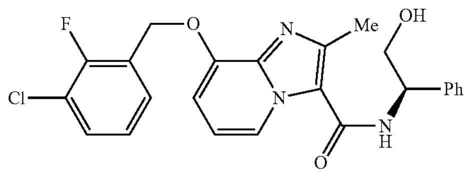
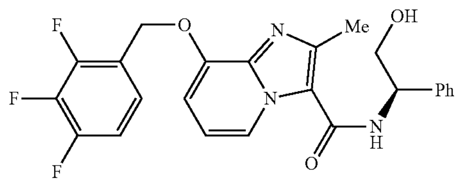
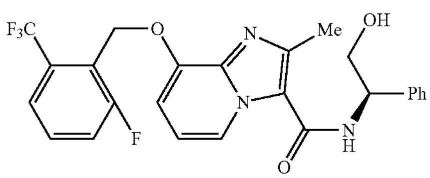
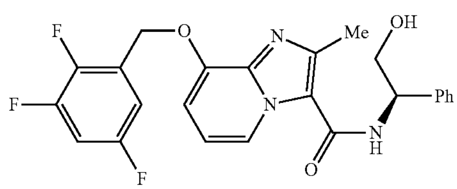
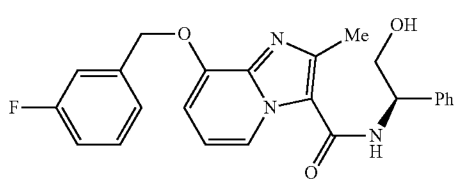
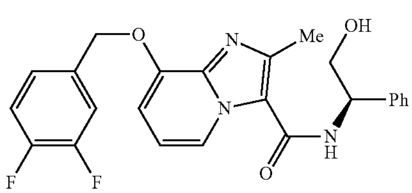
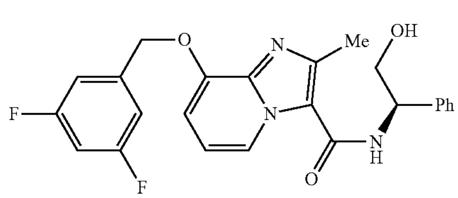
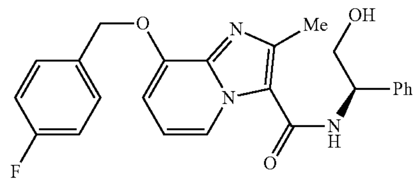
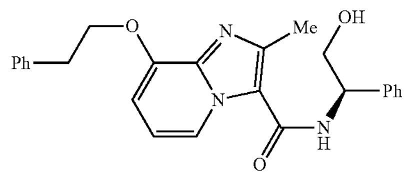
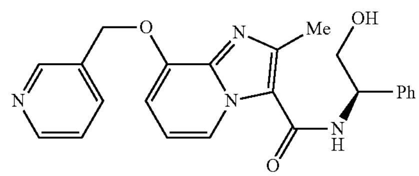
572	
573	
574	
575	
576	
577	
578	
579	
580	
581	
582	

TABLE 75

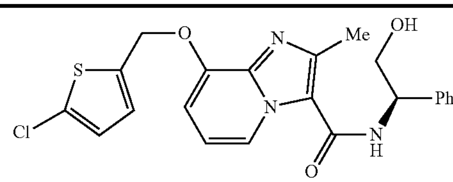
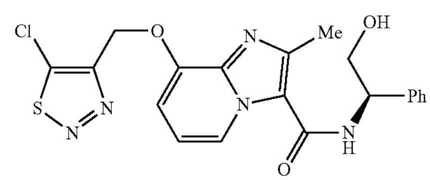
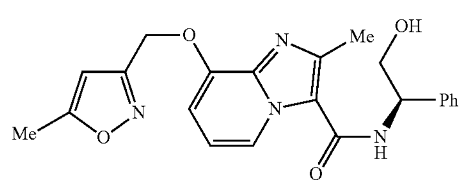
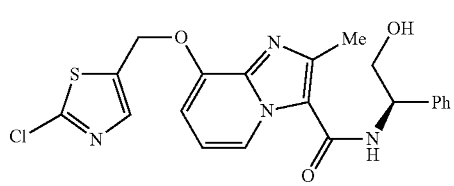
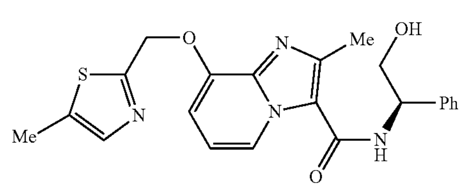
Ex	Str
583	
584	
585	
586	
587	

TABLE 75-continued

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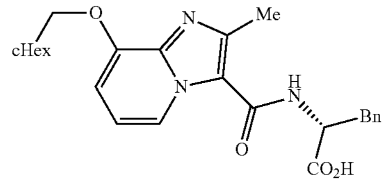
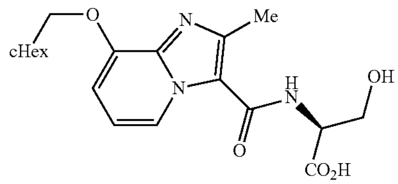
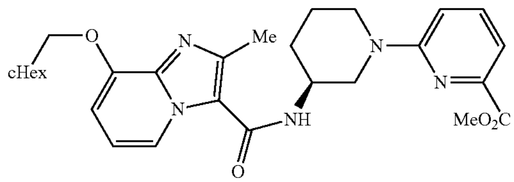
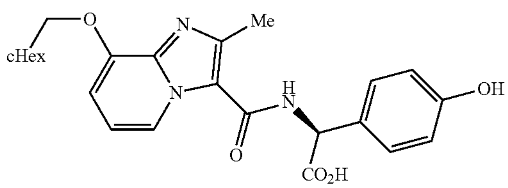
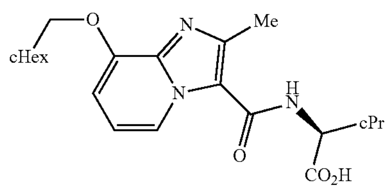
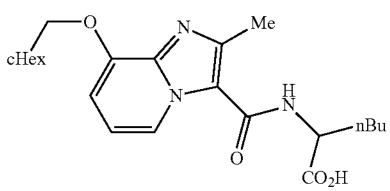
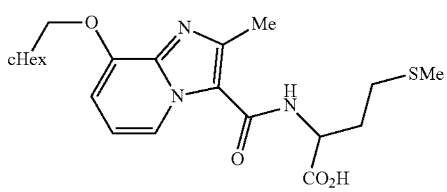
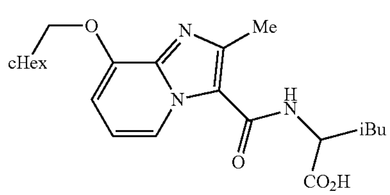
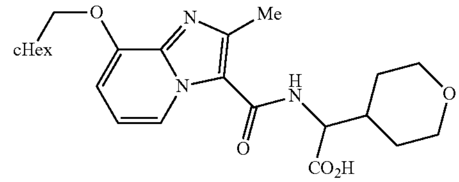
588	
589	
590	
591	
592	
593	
594	
595	
596	

TABLE 76

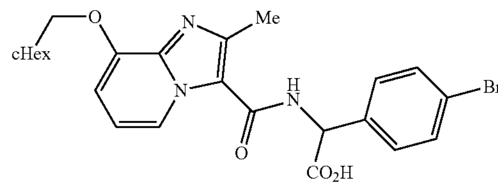
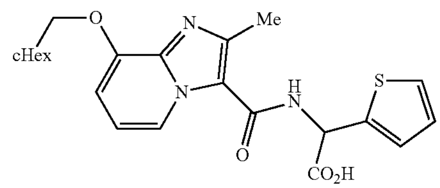
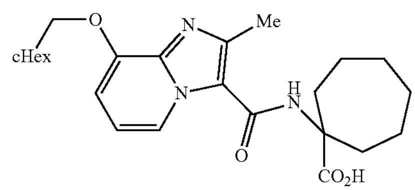
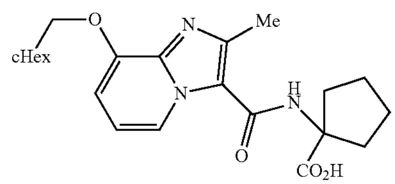
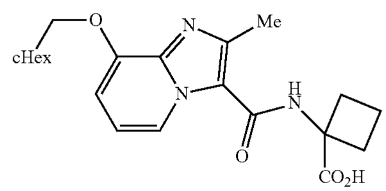
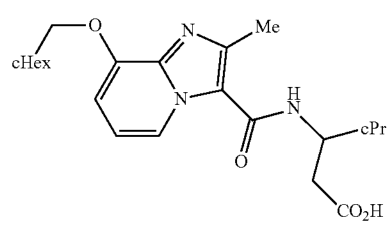
Ex	Str
597	
598	
599	
600	
601	
602	

TABLE 76-continued

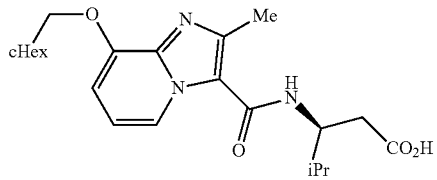
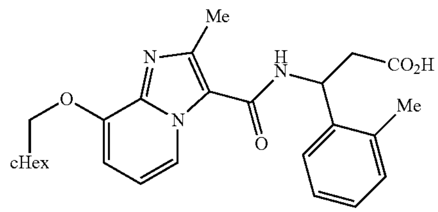
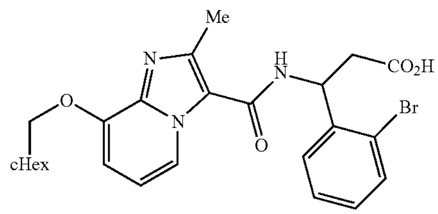
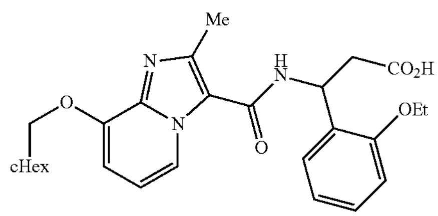
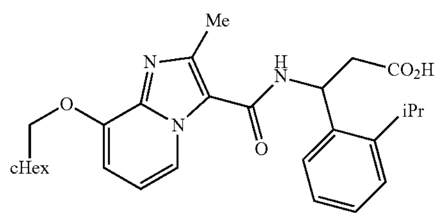
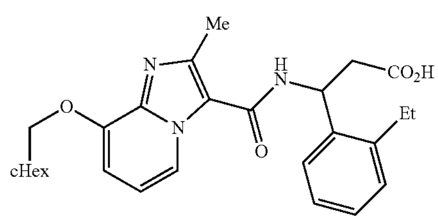
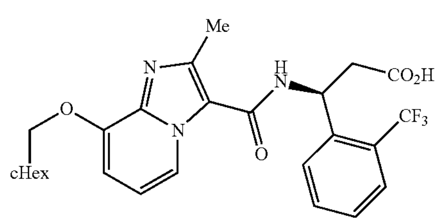
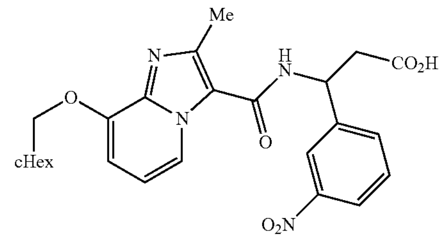
Ex	Str
603	
604	
605	
606	
607	
608	
609	
610	

TABLE 77

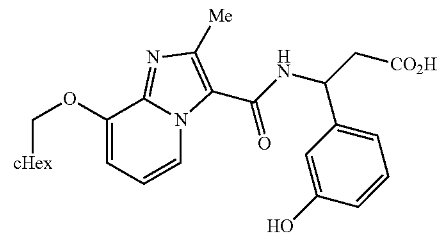
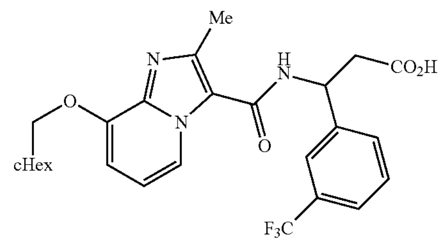
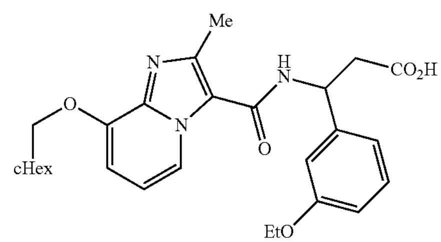
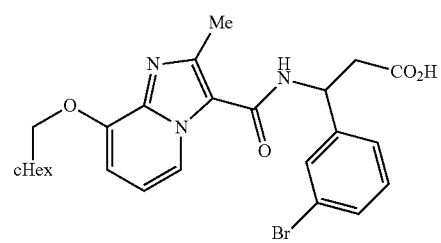
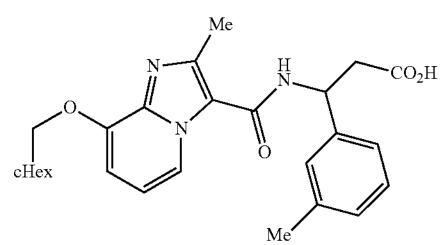
Ex	Str
611	
612	
613	
614	
615	

TABLE 77-continued

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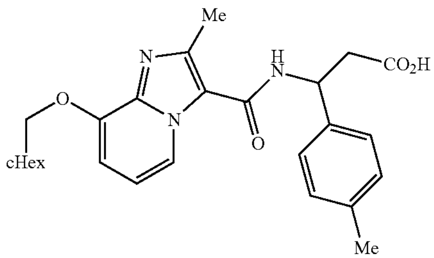
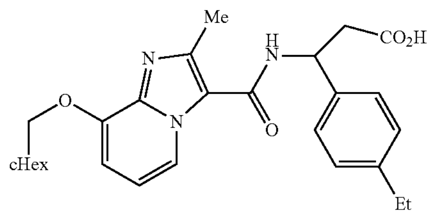
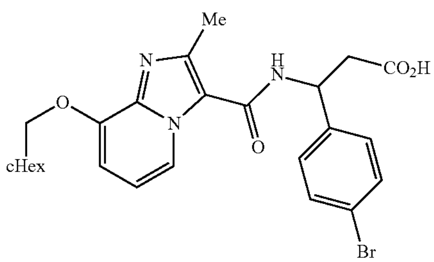
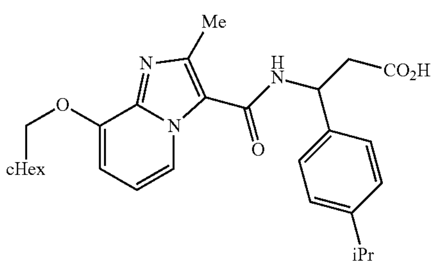
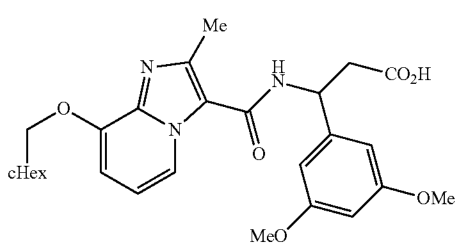
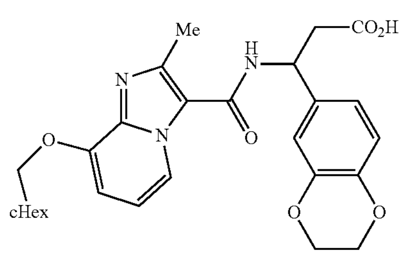
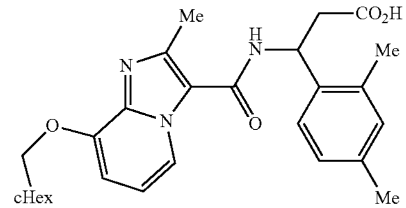
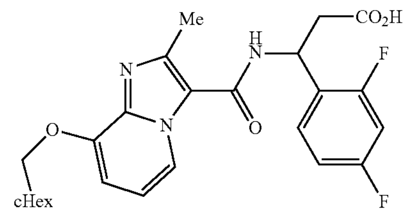
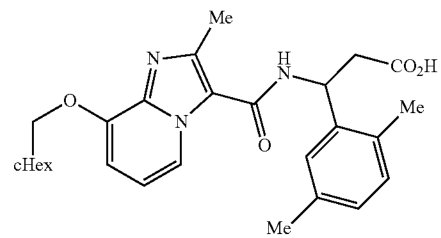
616	
617	
618	
619	
620	
621	
622	
623	
624	

TABLE 78

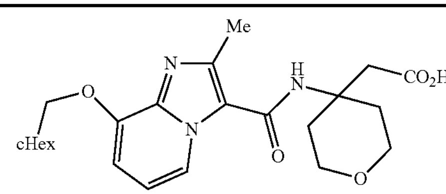
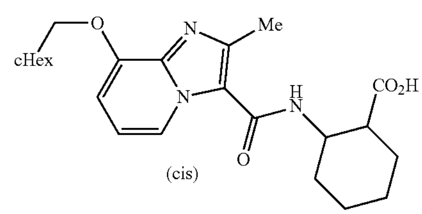
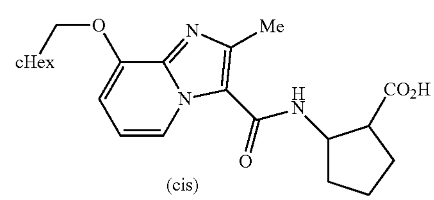
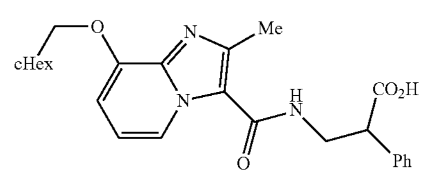
Ex	Str
625	
626	 (cis)
627	 (cis)
628	

TABLE 78-continued

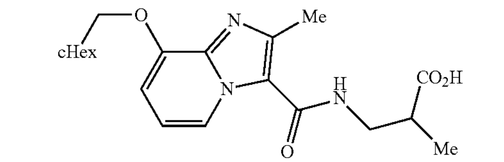
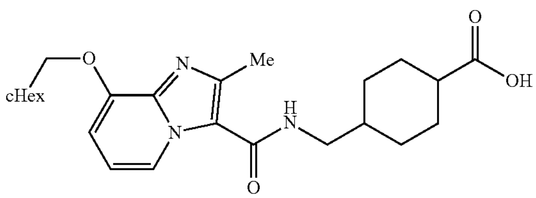
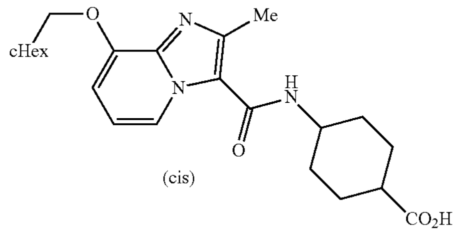
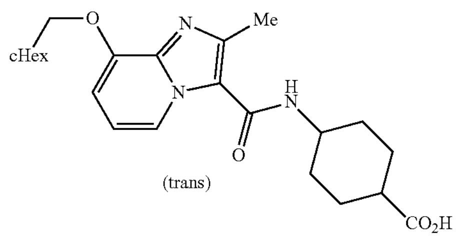
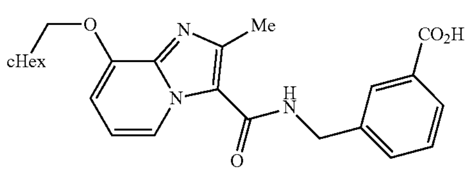
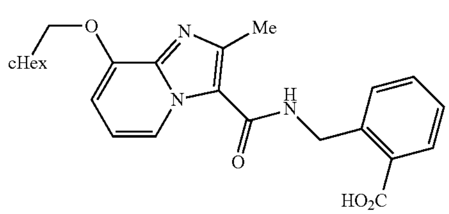
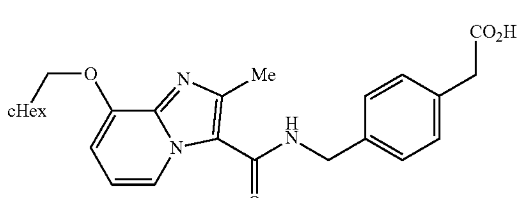
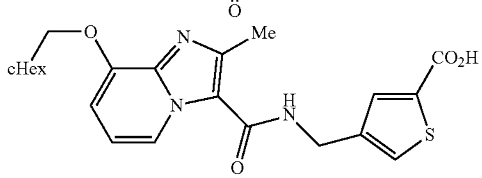
Ex	Str
629	
630	
631	
632	
633	
634	
635	
636	

TABLE 79

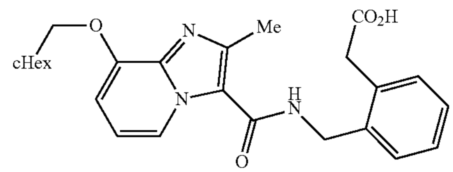
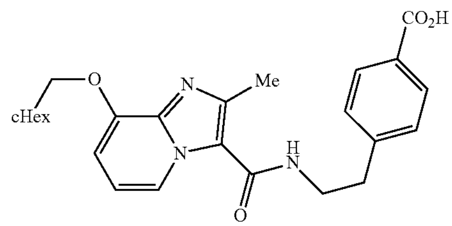
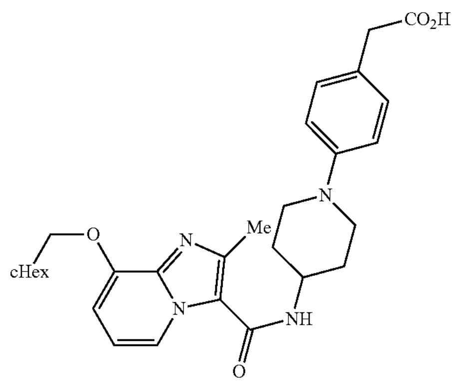
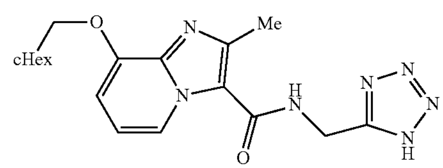
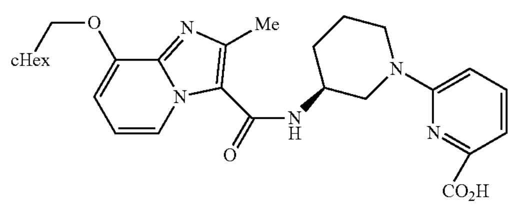
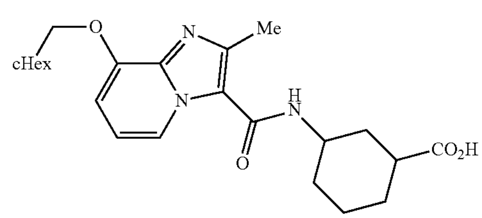
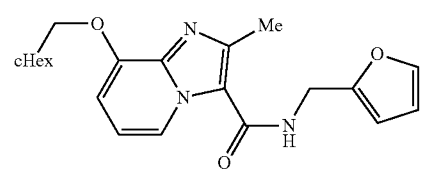
Ex	Str
637	
638	
639	
640	
641	
642	
643	

TABLE 79-continued

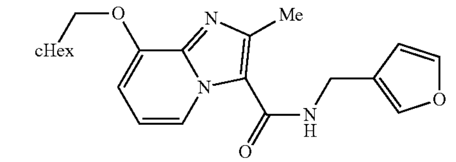
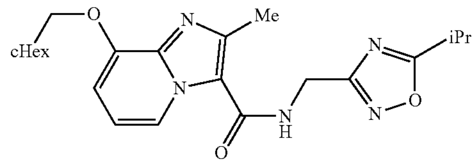
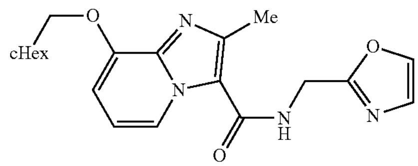
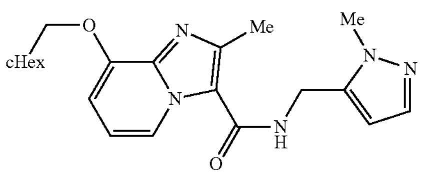
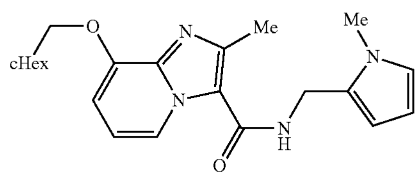
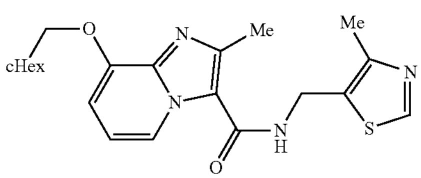
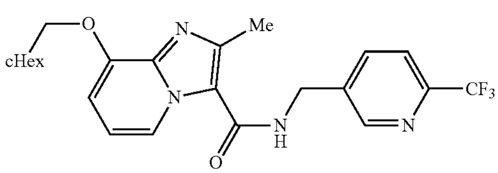
Ex	Str
644	
645	
646	
647	
648	
649	
650	

TABLE 80

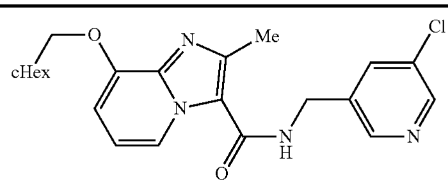
Ex	Str
651	

TABLE 80-continued

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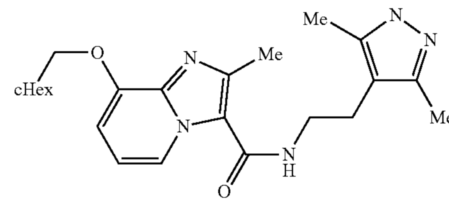
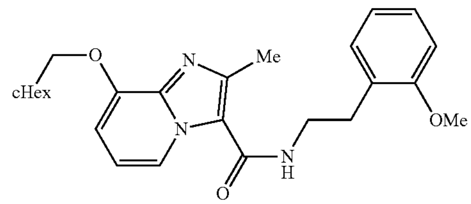
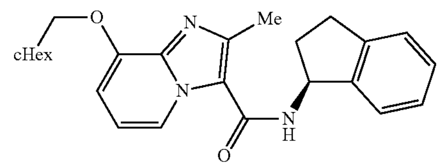
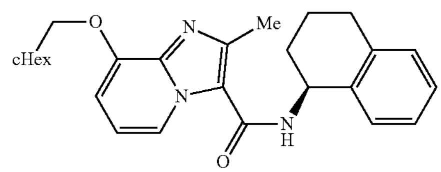
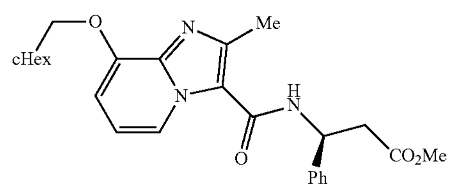
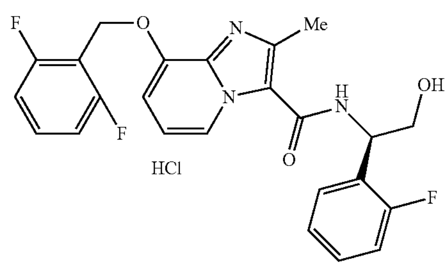
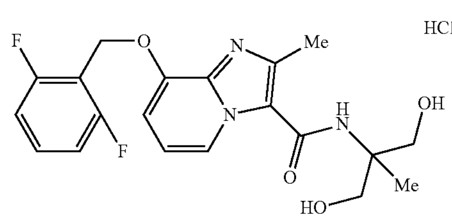
652	
653	
654	
655	
656	
657	
658	

TABLE 81

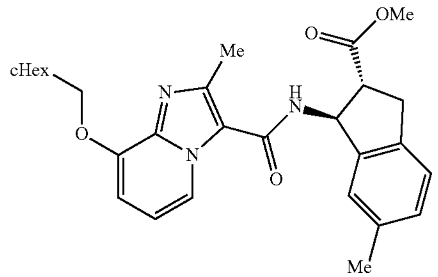
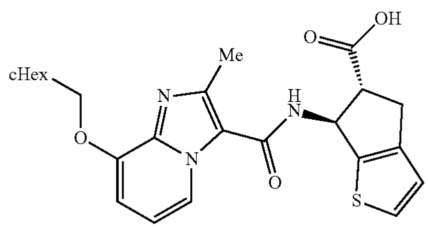
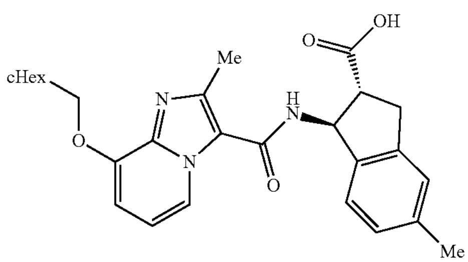
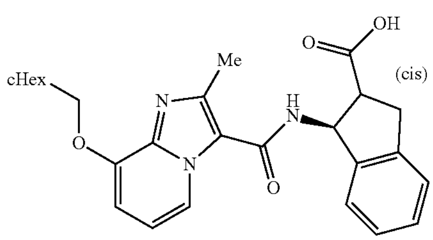
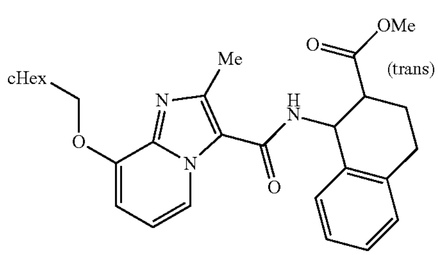
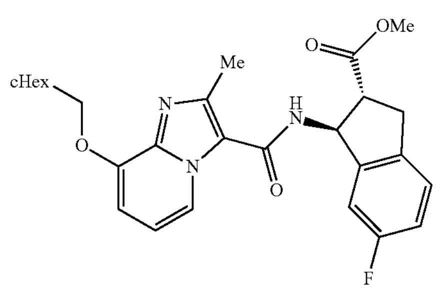
Ex	Str
659	
660	
661	
662	
663	
664	

TABLE 81-continued

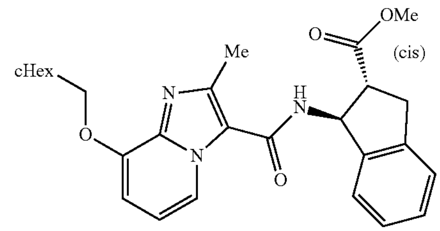
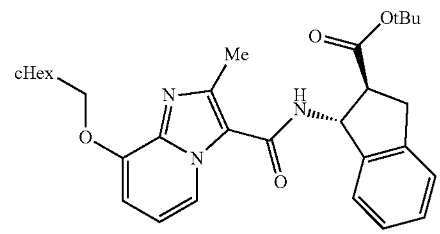
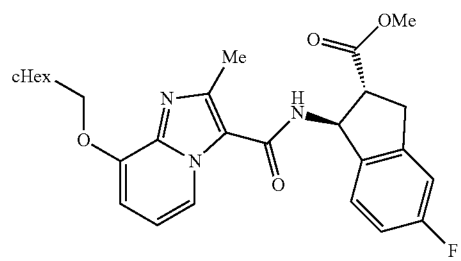
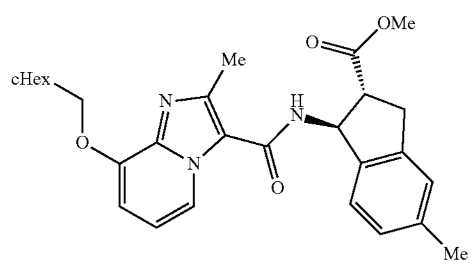
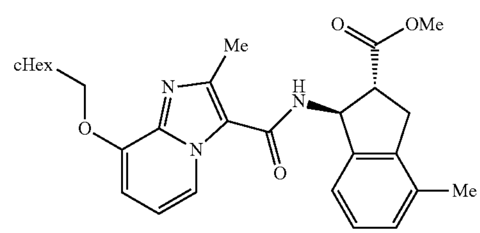
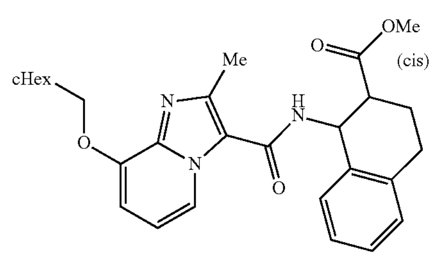
Ex	Str
665	
666	
667	
668	
669	
670	

TABLE 81-continued

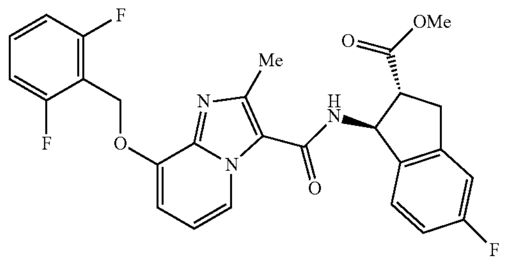
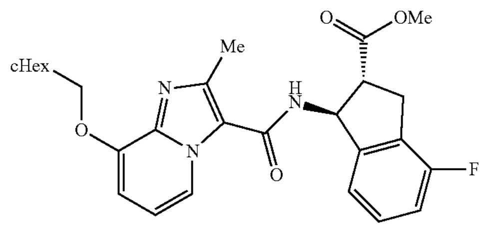
Ex	Str
671	
672	

TABLE 82

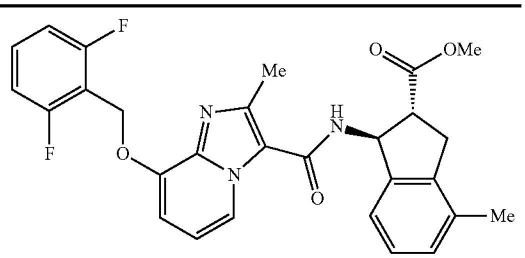
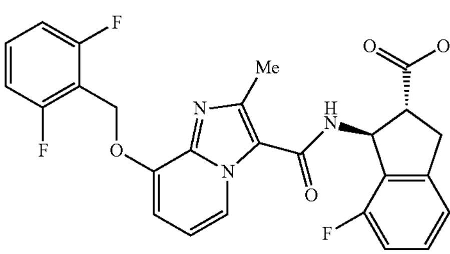
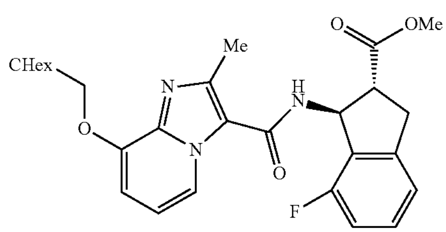
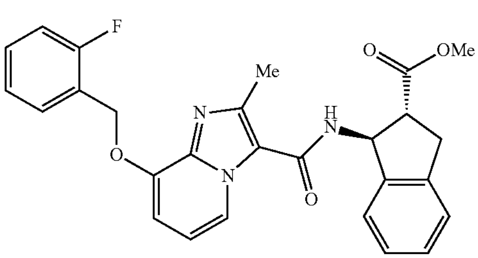
Ex	Str
673	
674	
675	
676	

TABLE 82-continued

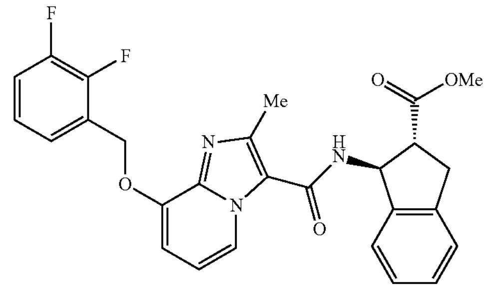
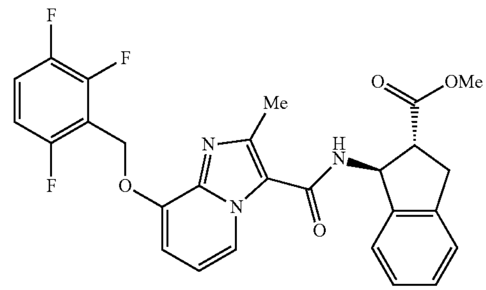
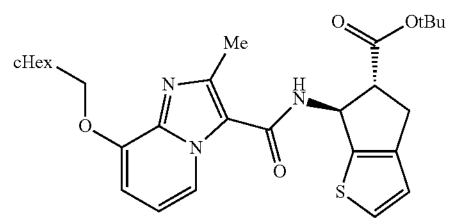
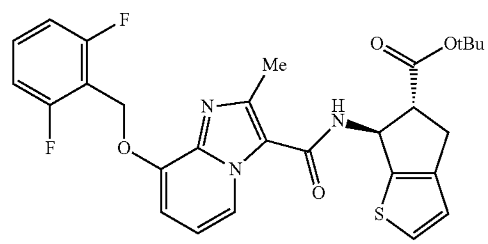
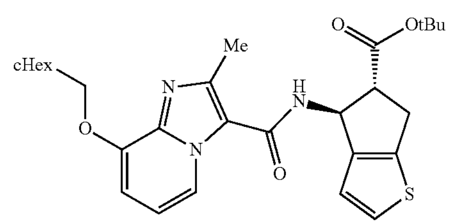
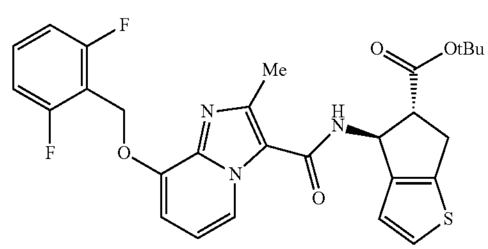
Ex	Str
677	
678	
679	
680	
681	
682	

TABLE 82-continued

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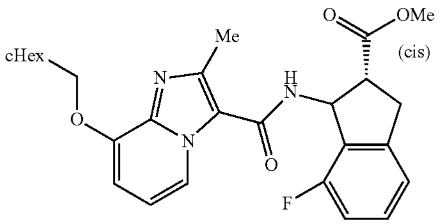
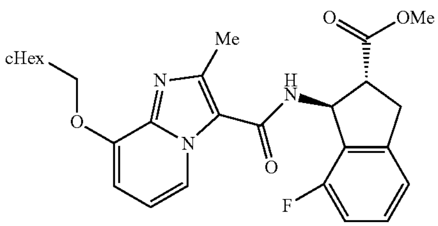
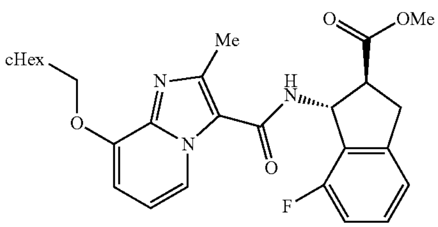
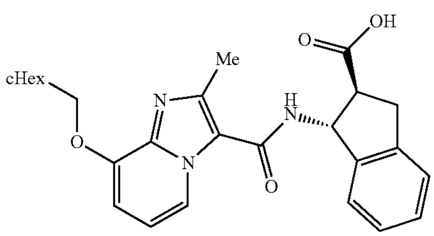
683	 (cis)
684	
685	
686	

TABLE 83

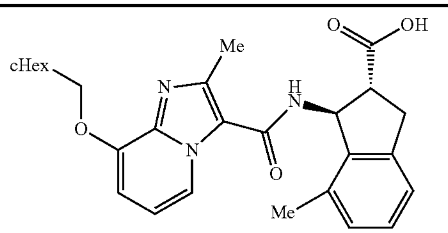
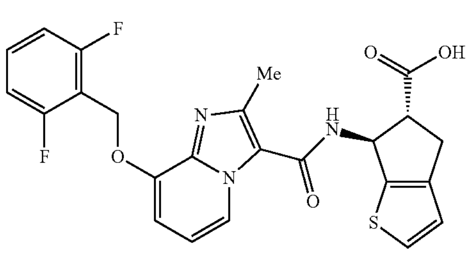
Ex	Str
687	
688	

TABLE 83-continued

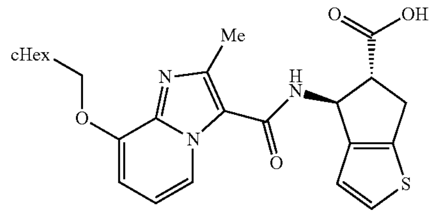
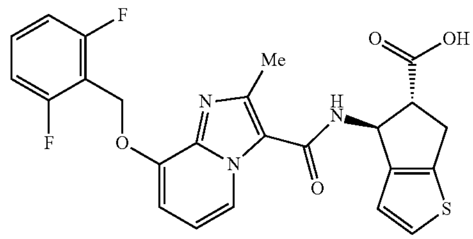
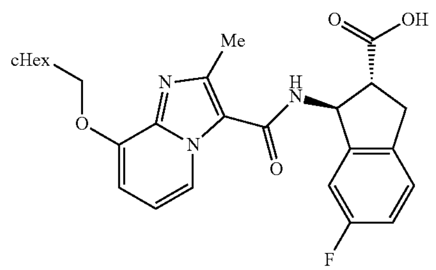
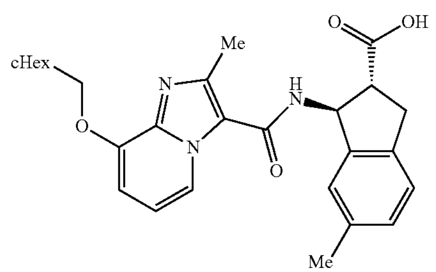
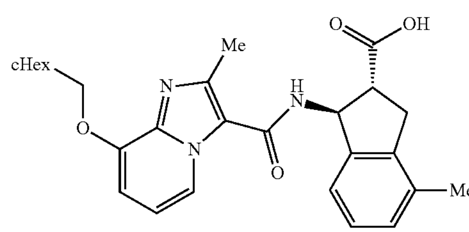
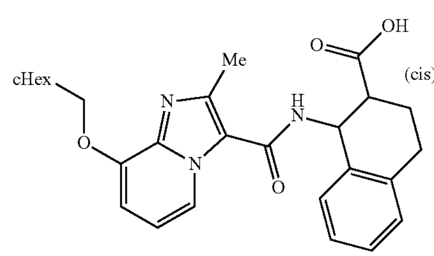
Ex	Str
689	
690	
691	
692	
693	
694	 (cis)

TABLE 83-continued

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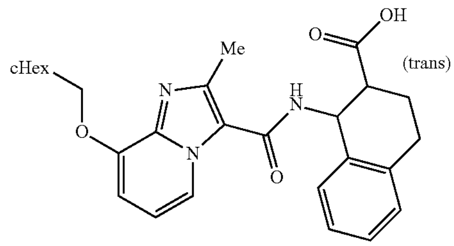
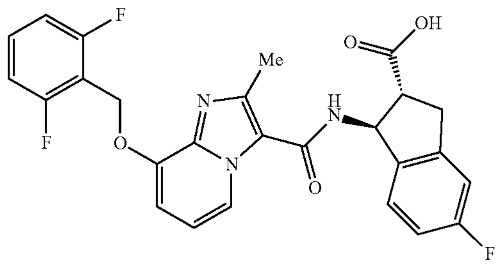
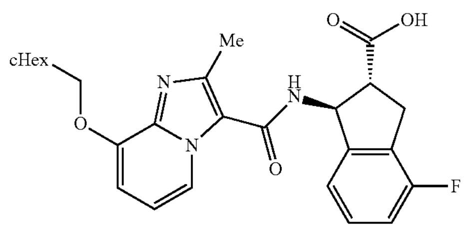
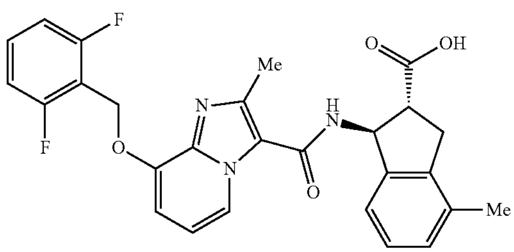
695	
696	
697	
698	

TABLE 84

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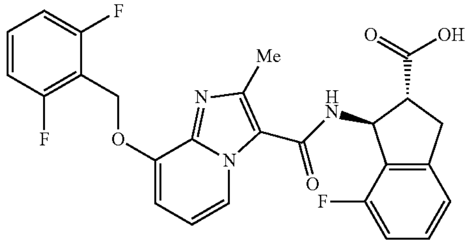
699	

TABLE 84-continued

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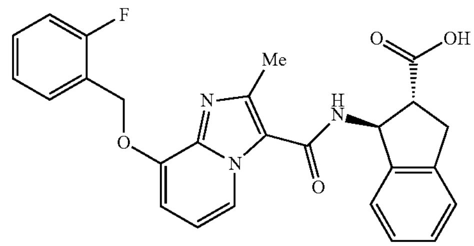
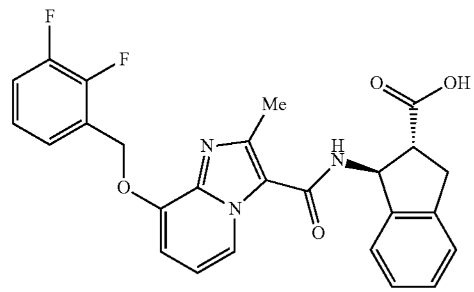
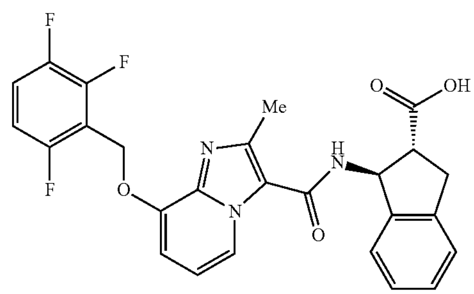
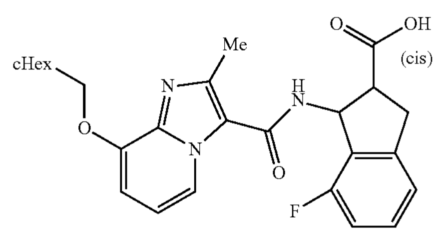
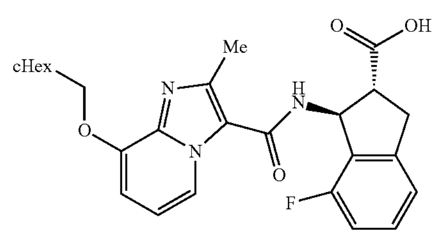
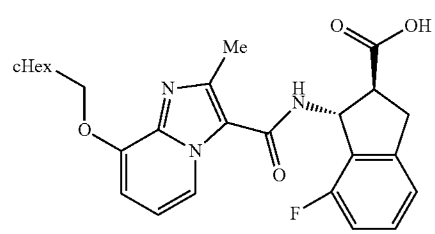
700	
701	
702	
703	
704	
705	

TABLE 84-continued

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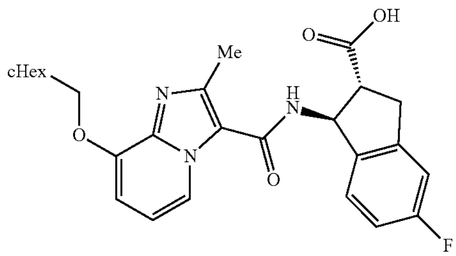
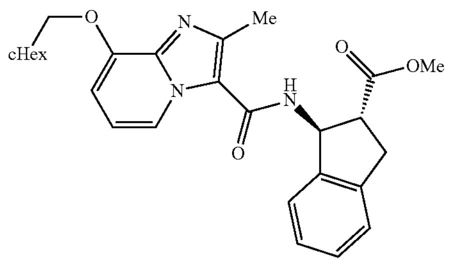
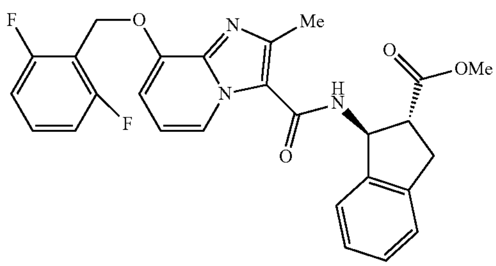
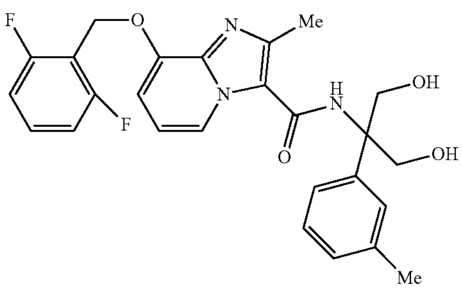
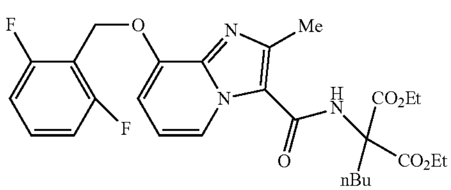
706	
707	
708	
709	
710	

TABLE 85

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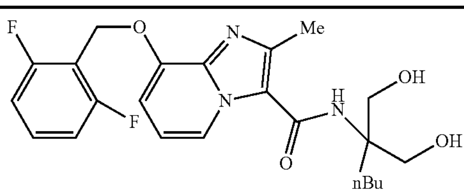
711	

TABLE 85-continued

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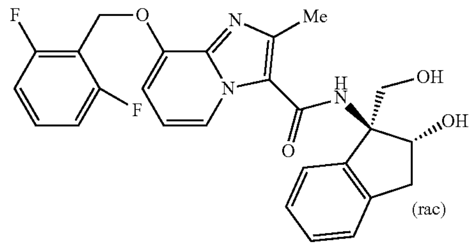
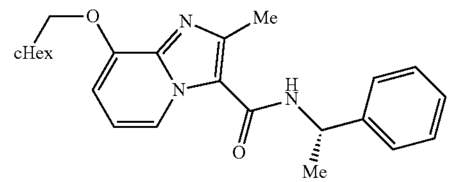
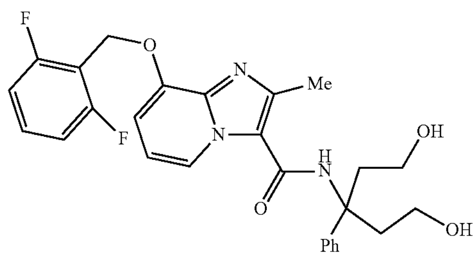
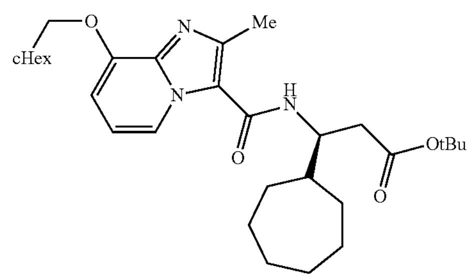
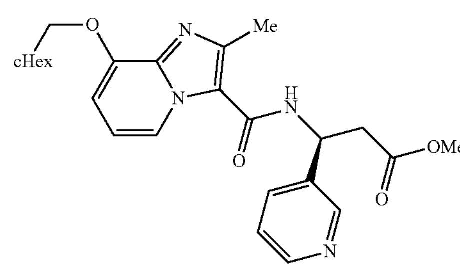
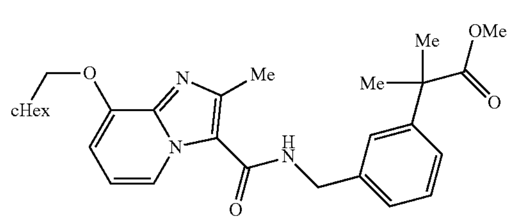
712	
713	
714	
715	
716	
717	

TABLE 85-continued

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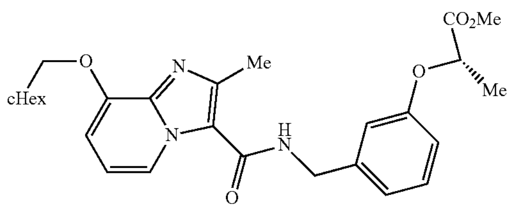
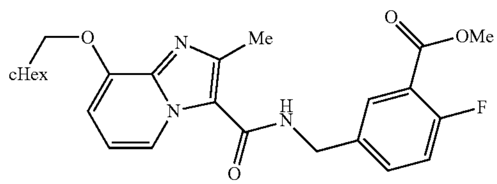
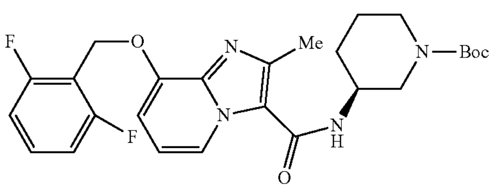
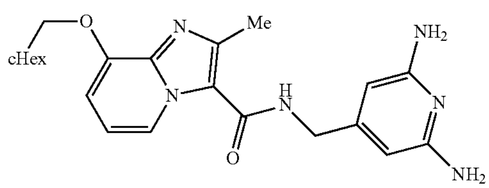
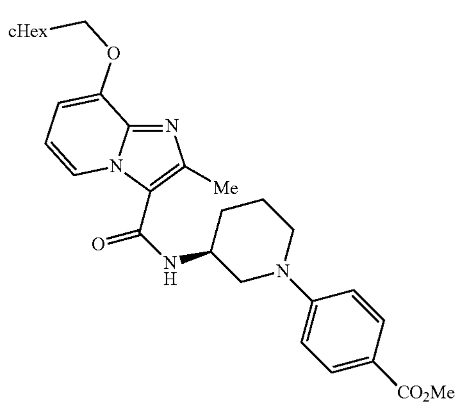
718	
719	
720	
721	
722	

TABLE 86

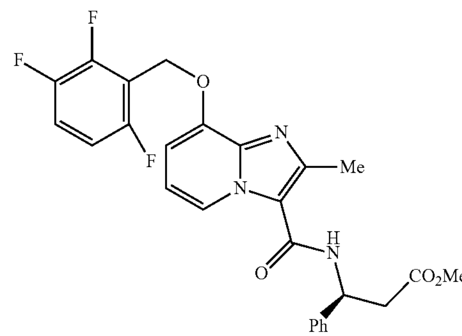
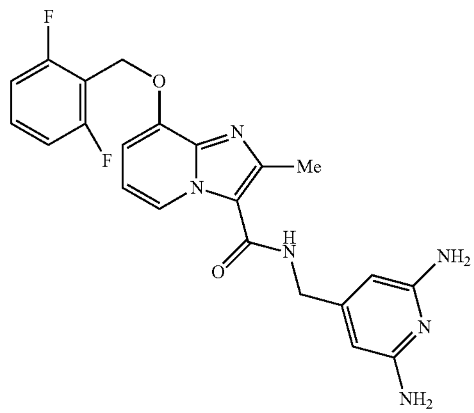
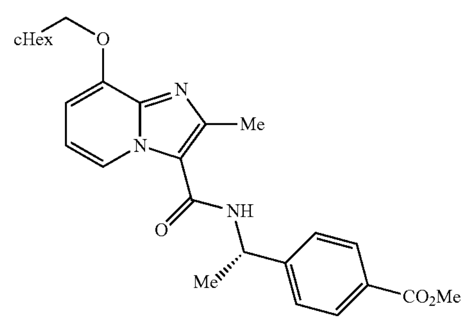
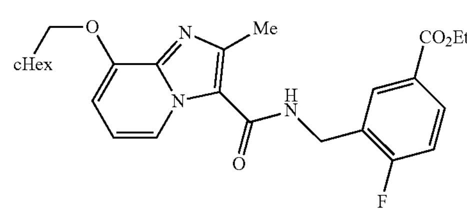
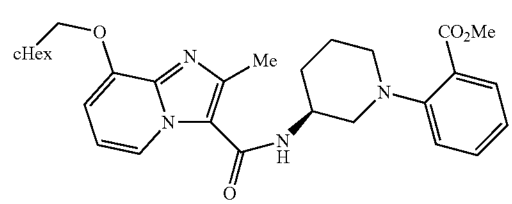
Ex	Str
723	
724	
725	
726	
727	

TABLE 86-continued

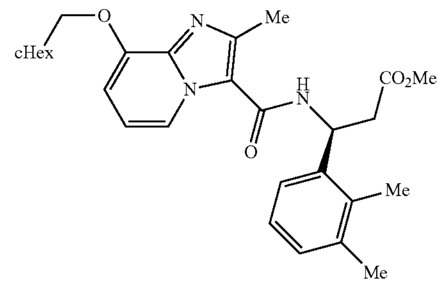
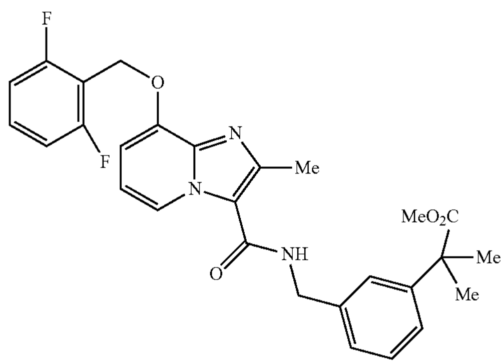
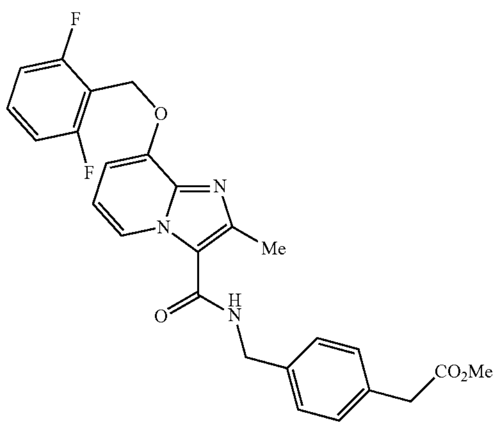
Ex	Str
728	
729	
730	

TABLE 87

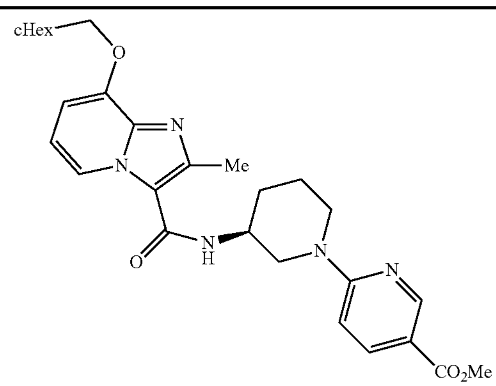
Ex	Str
731	

TABLE 87-continued

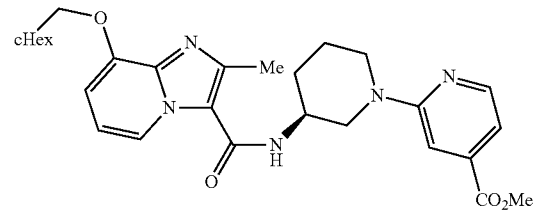
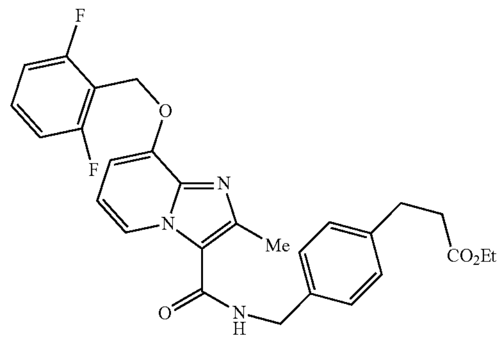
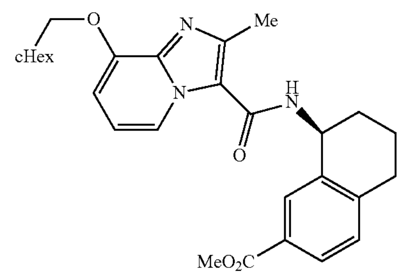
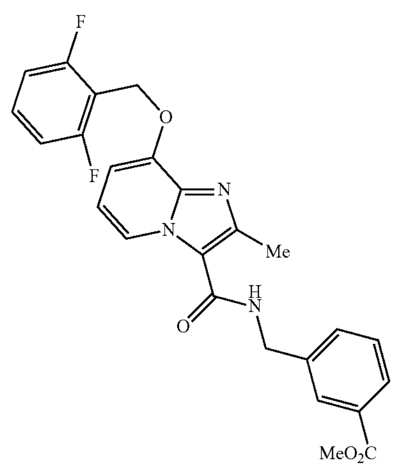
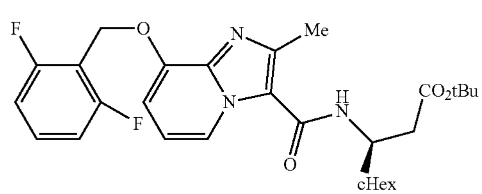
Ex	Str
732	
733	
734	
735	
736	

TABLE 87-continued

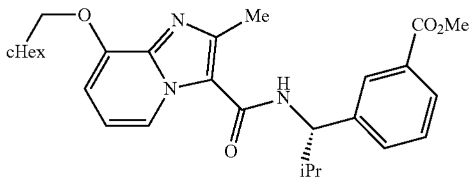
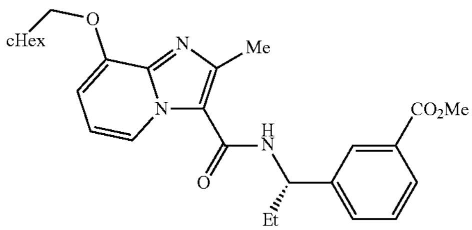
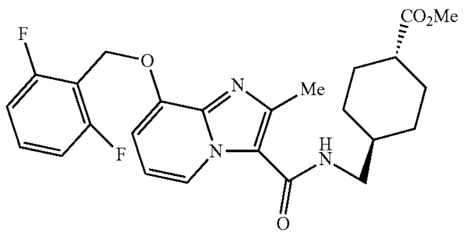
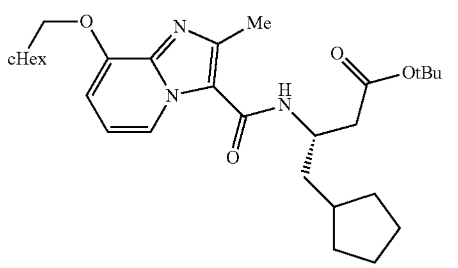
Ex	Str
737	
738	
739	
740	

TABLE 88

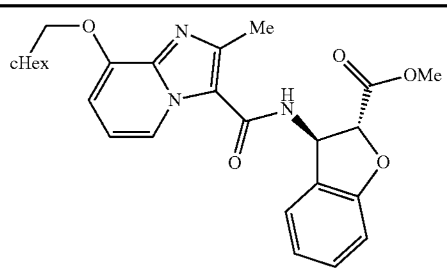
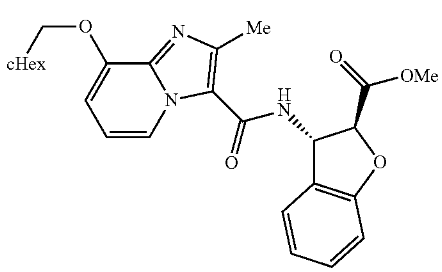
Ex	Str
741	
742	

TABLE 88-continued

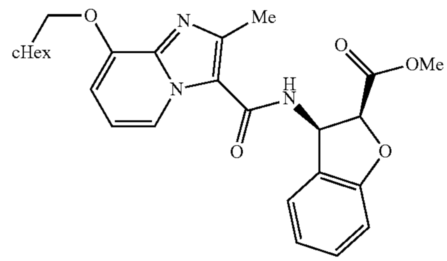
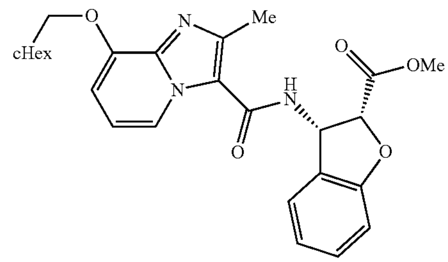
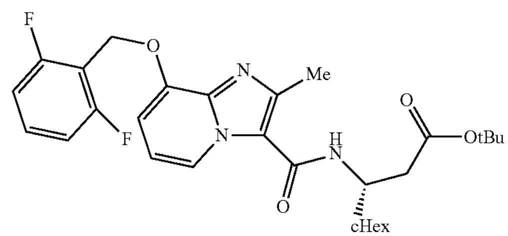
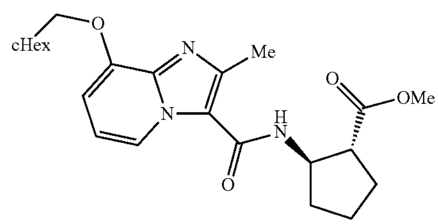
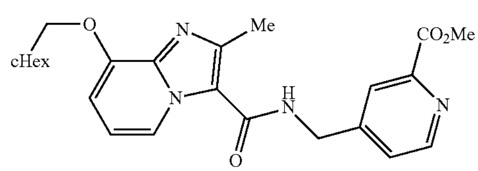
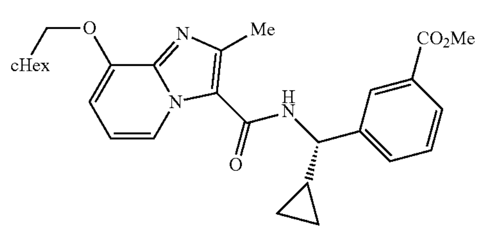
Ex	Str
743 744	 or 
745	
746	
747	
748	

TABLE 88-continued

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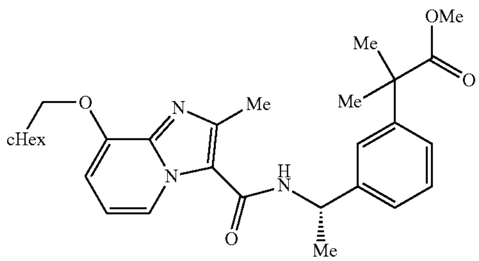
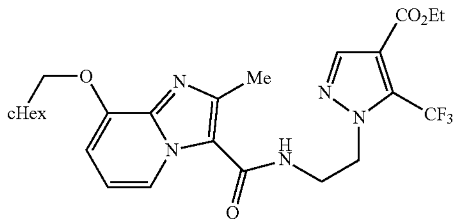
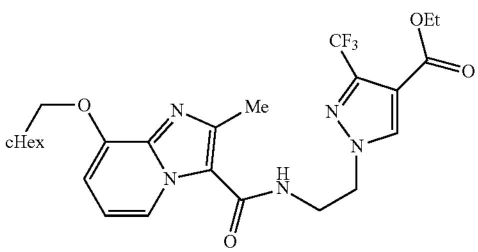
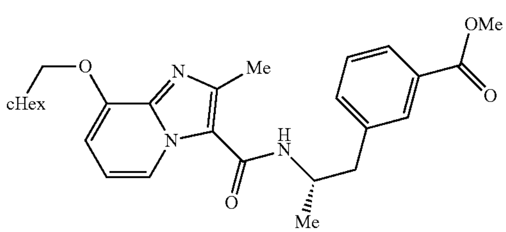
749	
750	
751	
752	

TABLE 89

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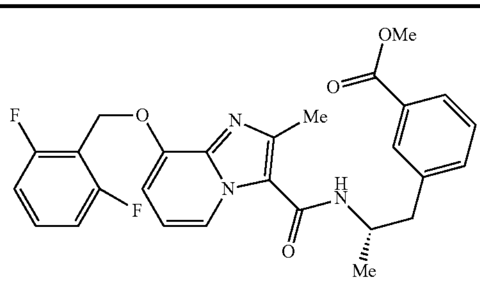
753	

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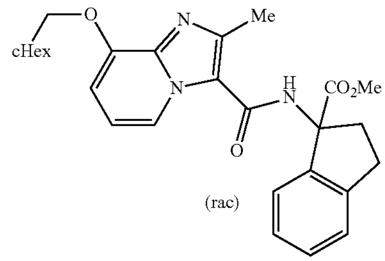
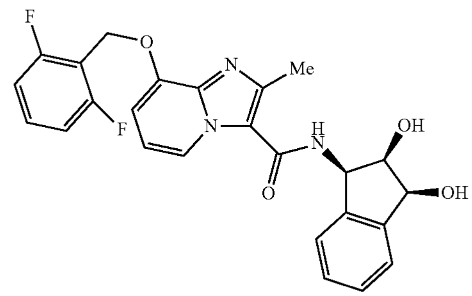
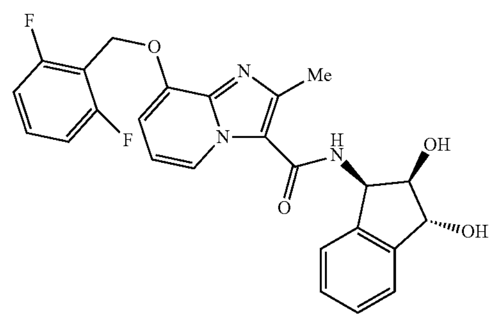
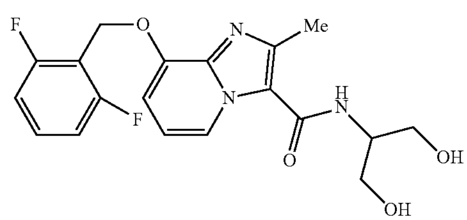
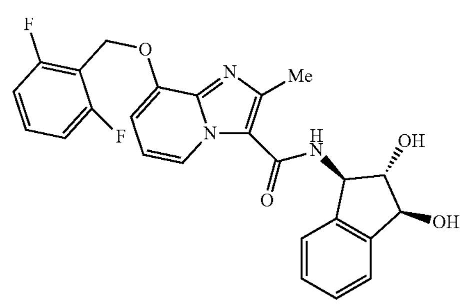
754	
755 756	 or 
757	
758 759	 or

TABLE 89-continued

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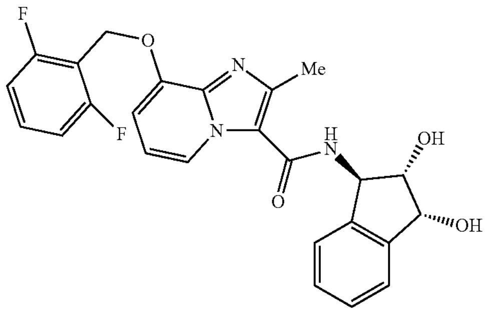
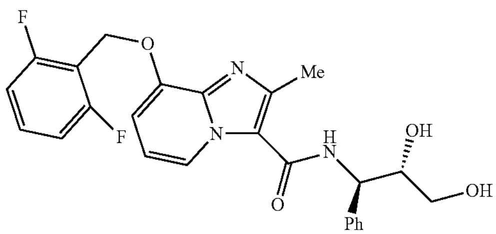
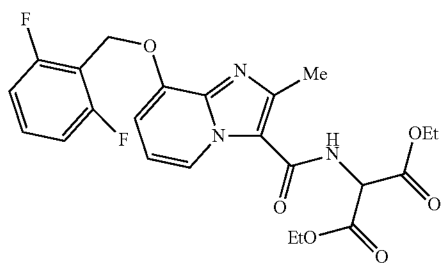
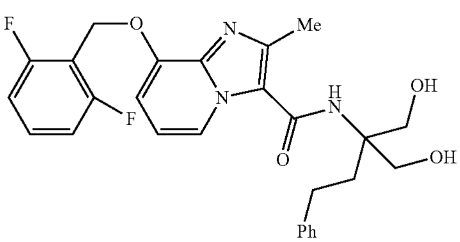
	
760	
761	
762	

TABLE 90

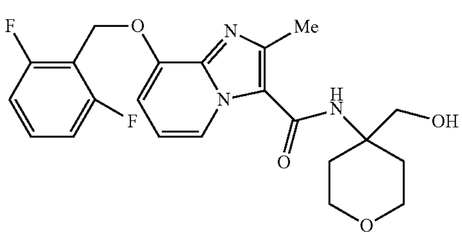
Ex	Str
763	

TABLE 90-continued

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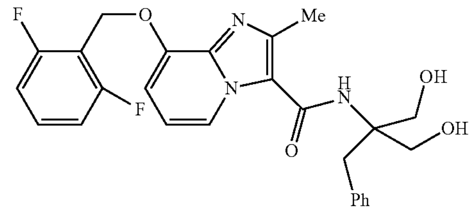
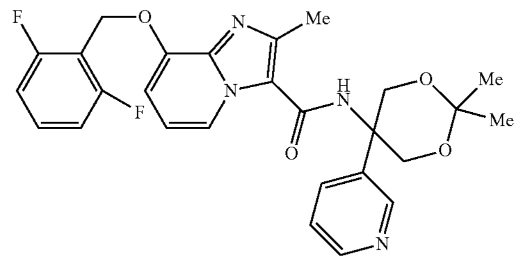
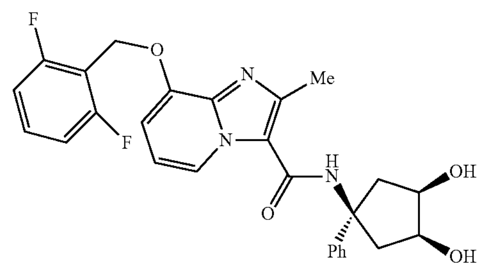
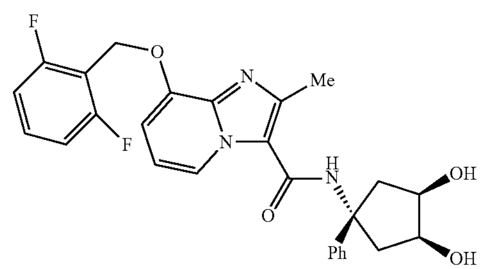
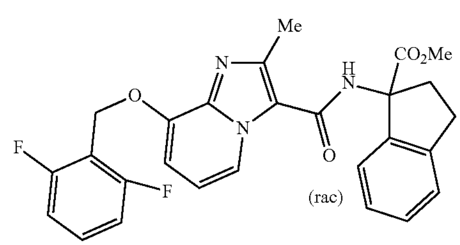
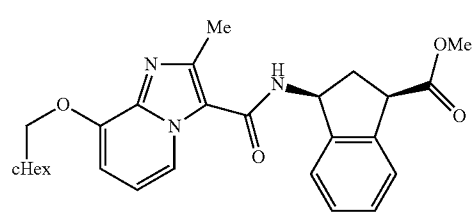
764	
765	
766 767	 or 
768	
769 770	 or

TABLE 90-continued

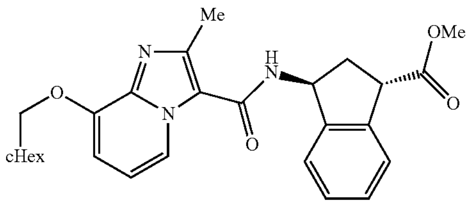
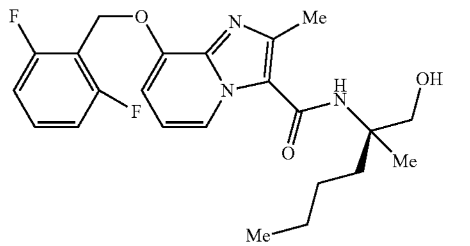
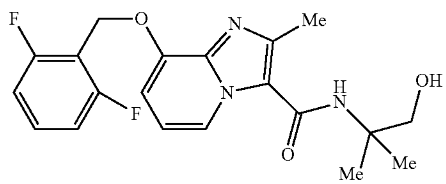
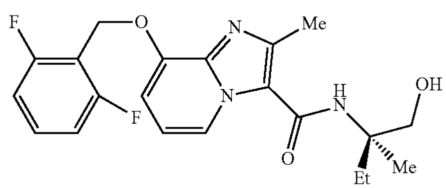
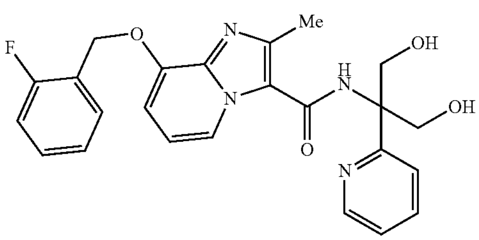
Ex	Str
	
771	
772	
773	
774	

TABLE 91

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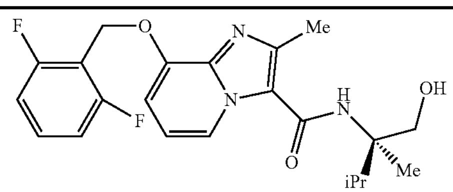
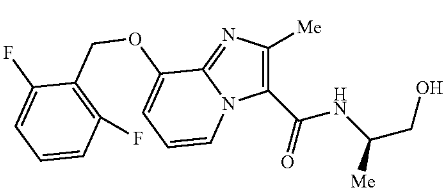
775	
776	

TABLE 91-continued

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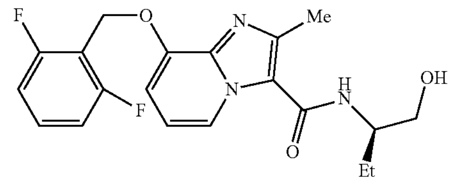
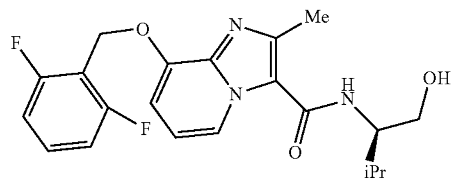
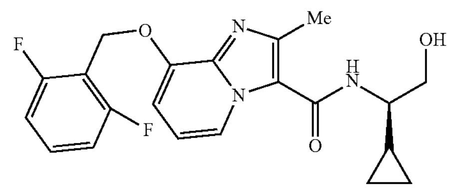
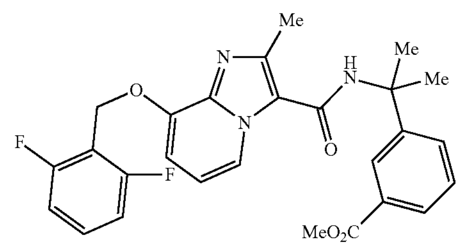
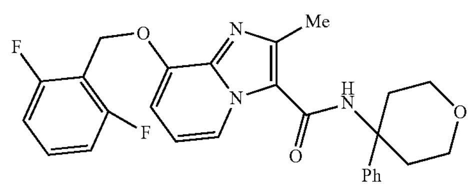
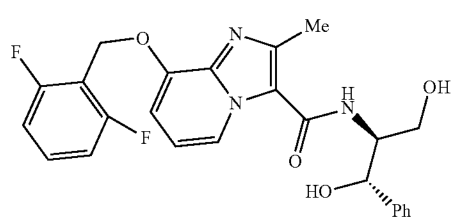
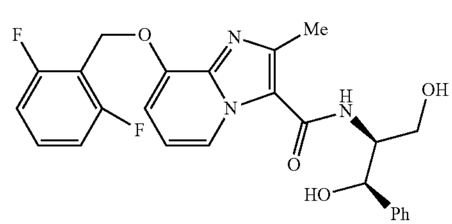
777	
778	
779	
780	
781	
782	
783	

TABLE 91-continued

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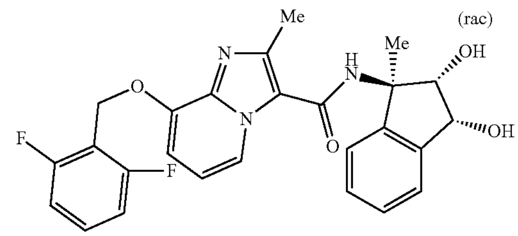
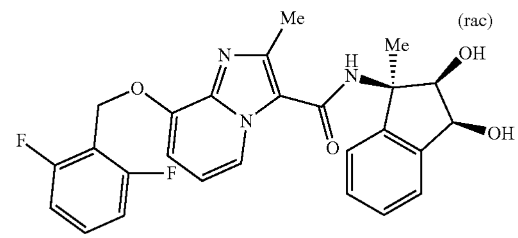
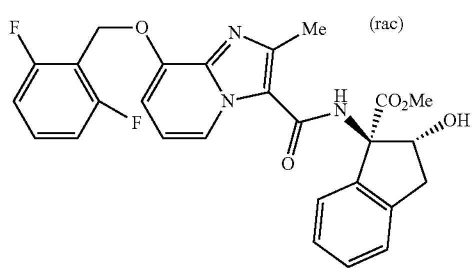
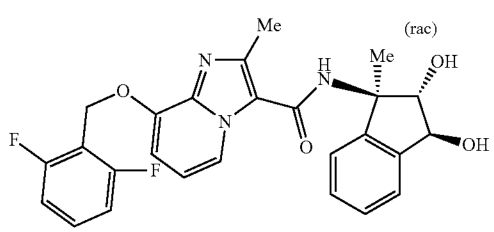
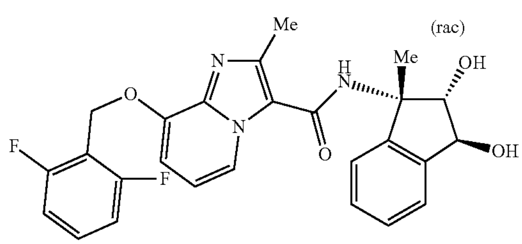
784	
785	
788	
786	 or 

TABLE 92

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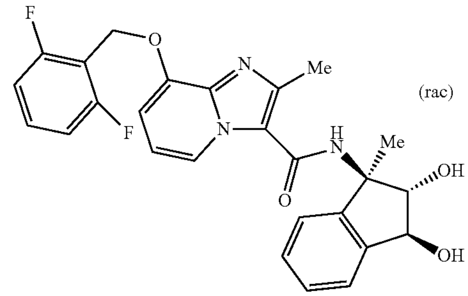
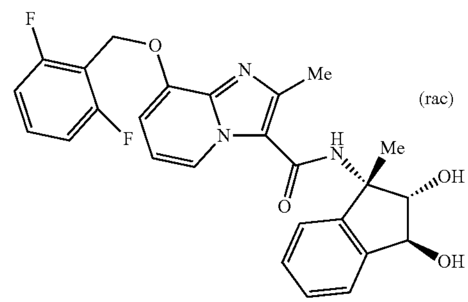
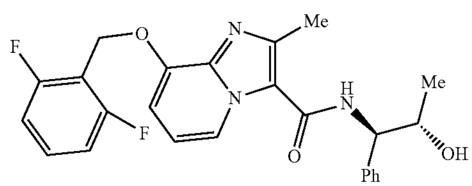
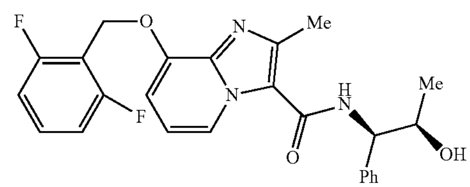
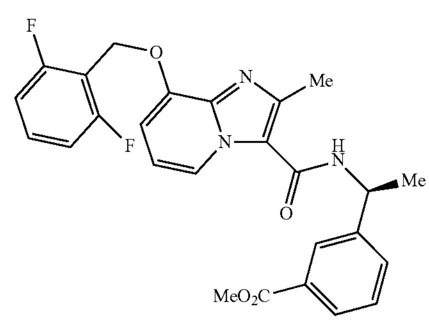
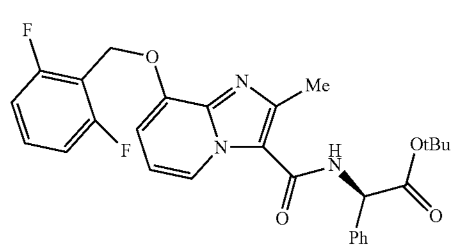
787	 or 
789	
790	
791	
792	

TABLE 92-continued

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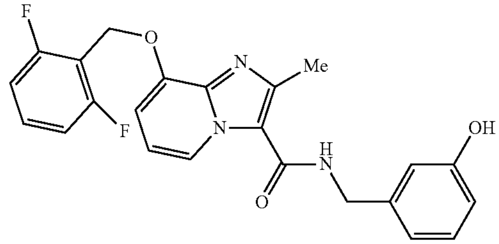
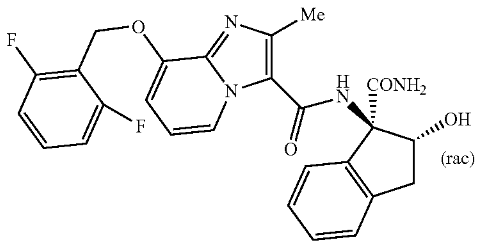
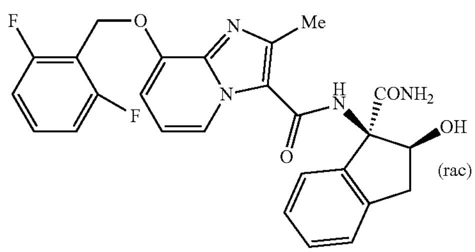
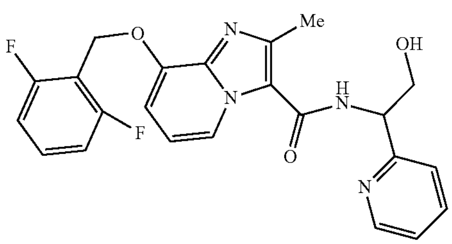
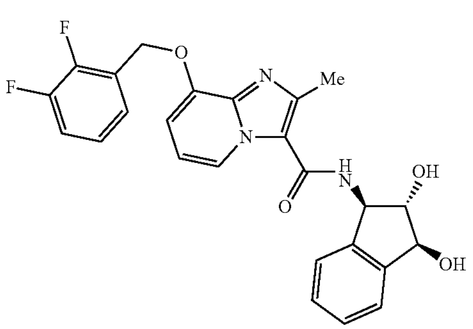
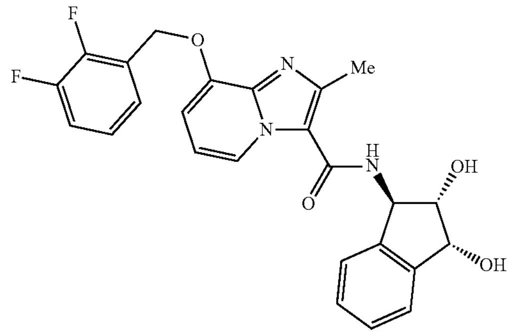
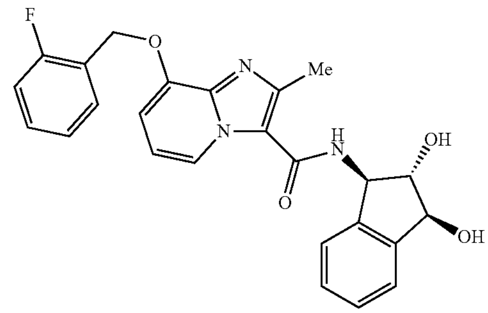
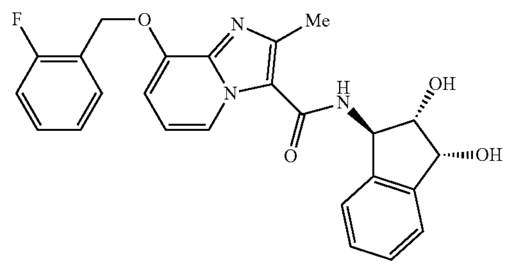
793	
794	
795	
796	
797	 or 
798	 or 

TABLE 93

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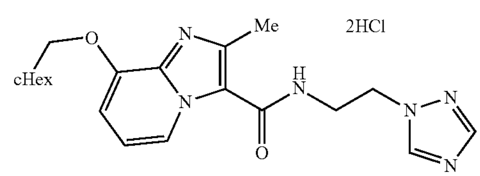
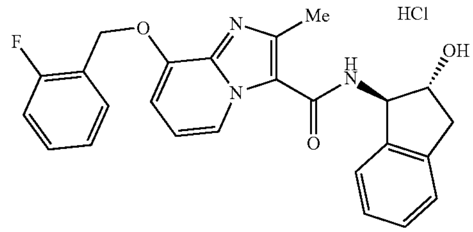
799	 2HCl
800	 HCl

TABLE 93-continued

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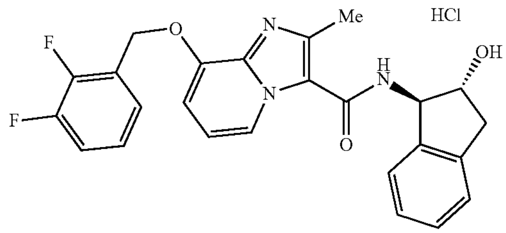
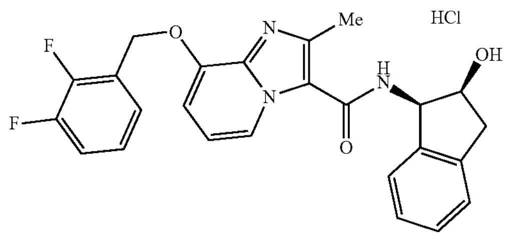
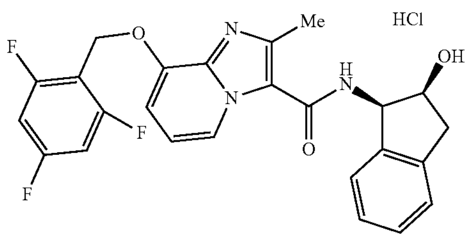
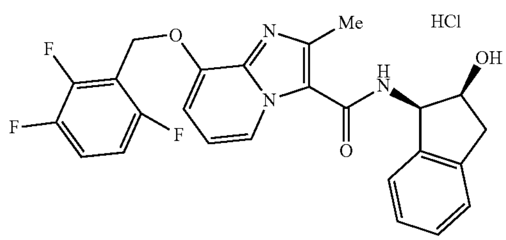
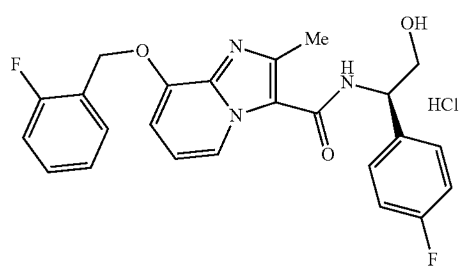
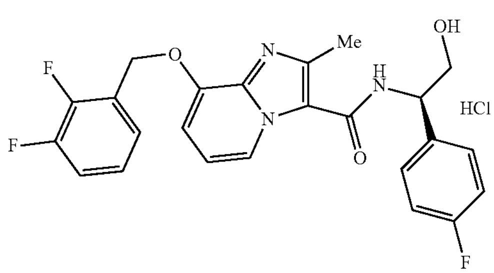
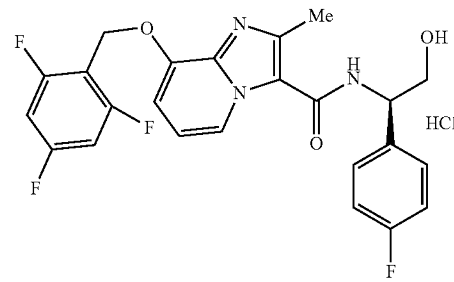
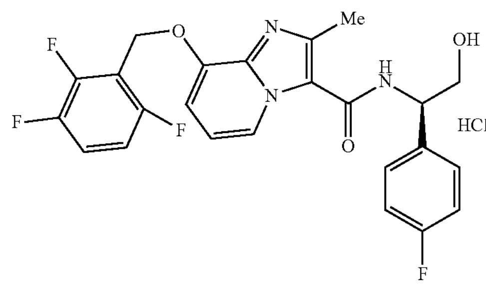
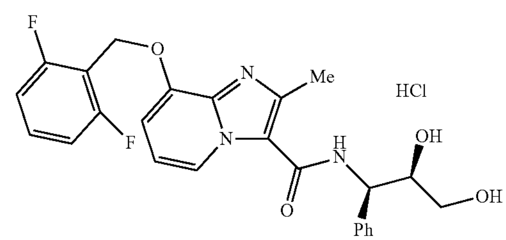
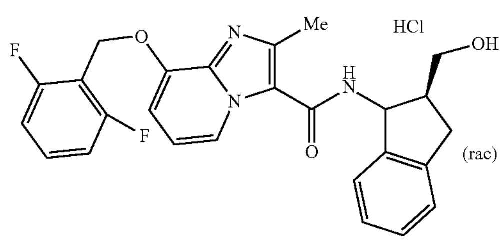
801	
802	
803	
804	
805	
806	
807	
808	
809	
810	

TABLE 94

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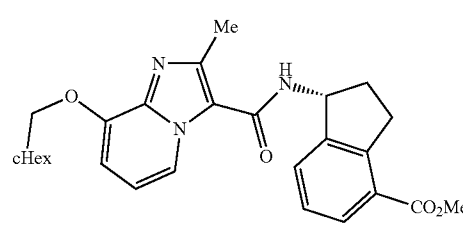
811	

TABLE 94-continued

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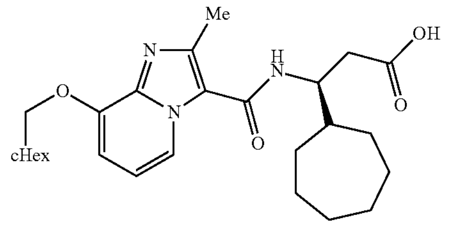
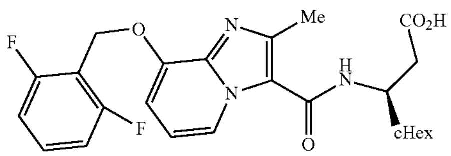
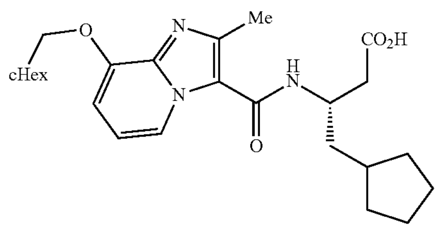
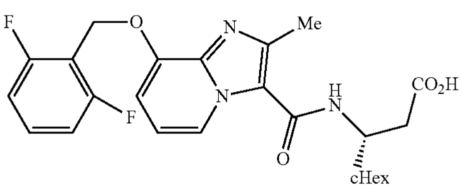
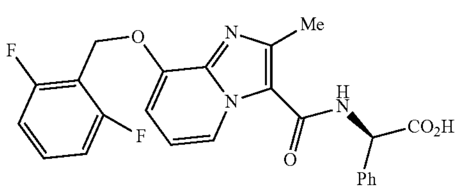
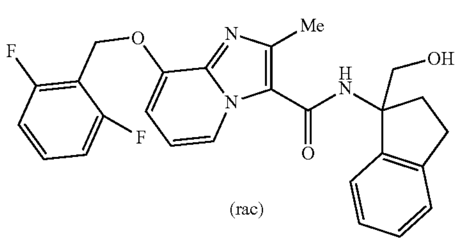
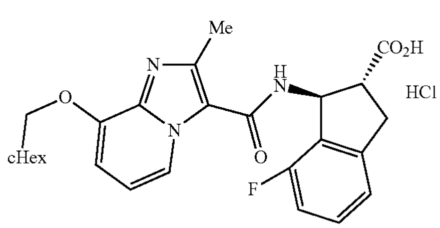
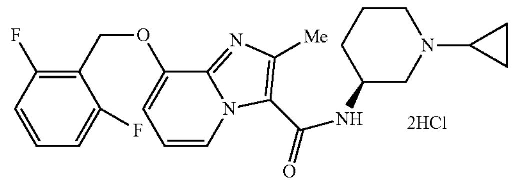
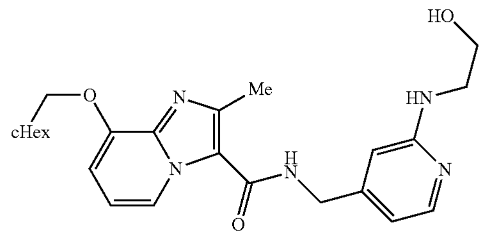
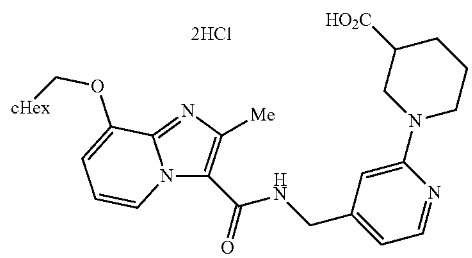
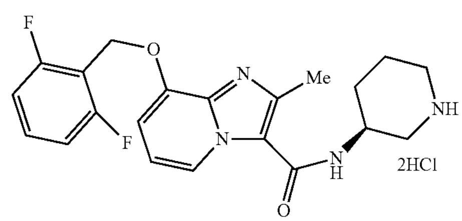
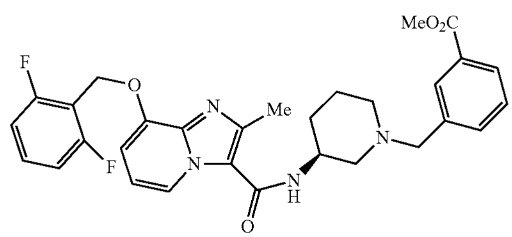
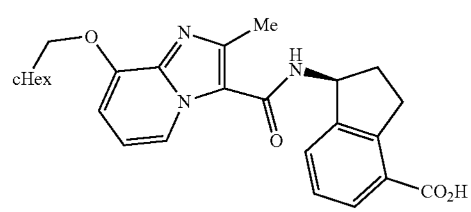
812	
813	
814	
815	
816	
817	
818	
819	
820	
821	
822	
823	
824	

TABLE 95

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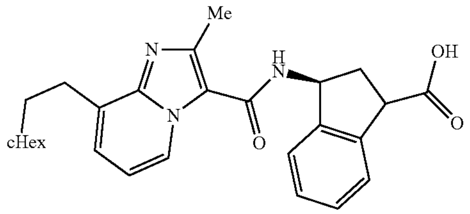
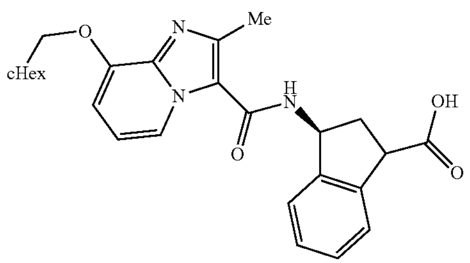
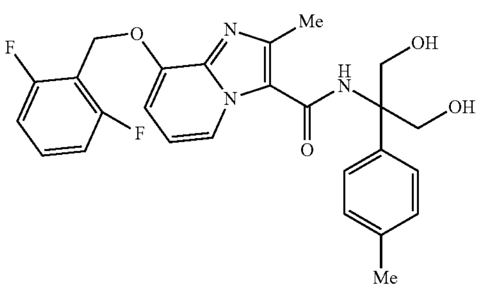
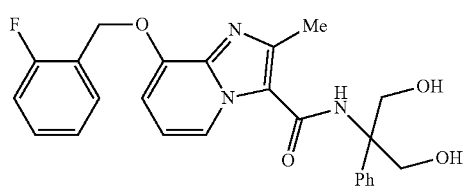
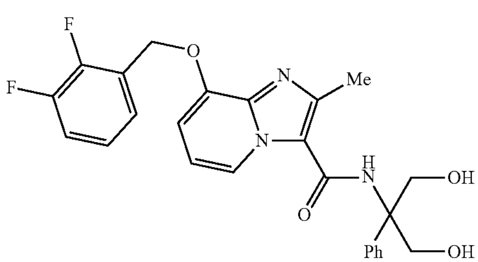
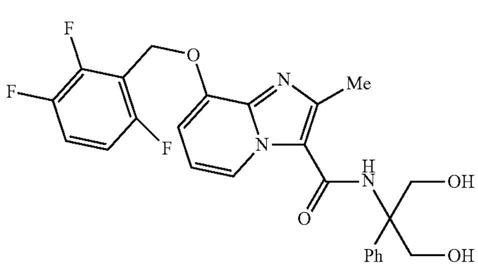
825	
826	
827	
828	
829	
830	

TABLE 95-continued

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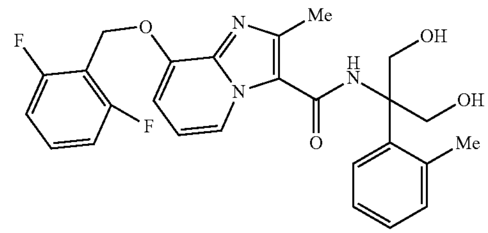
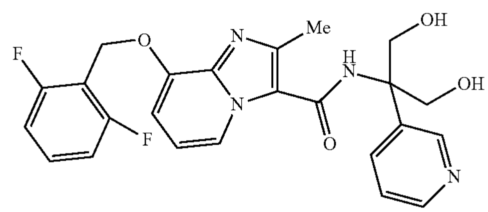
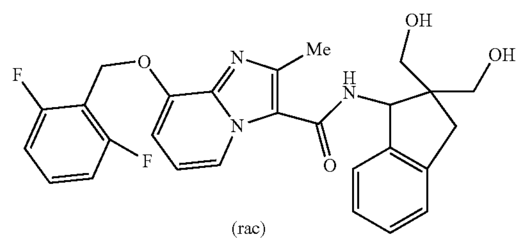
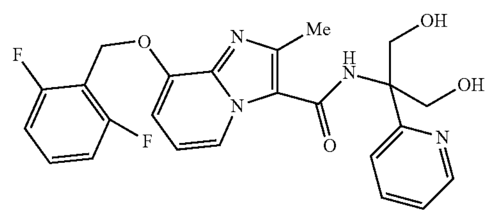
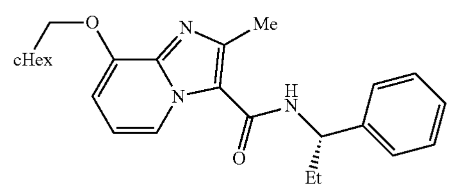
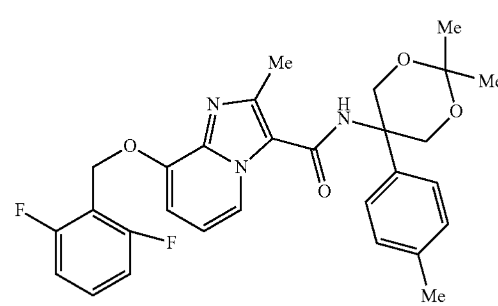
831	
832	
833	 (rac)
834	
835	
836	

TABLE 96

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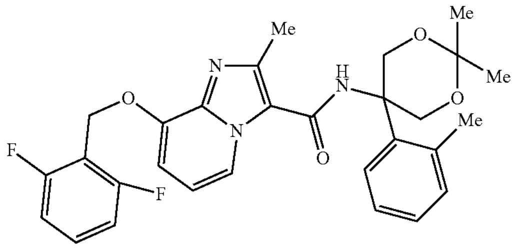
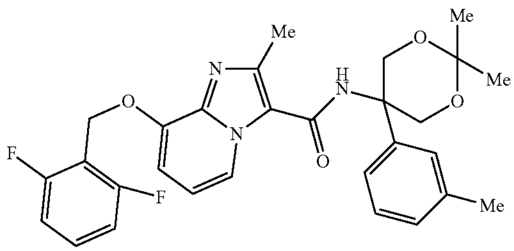
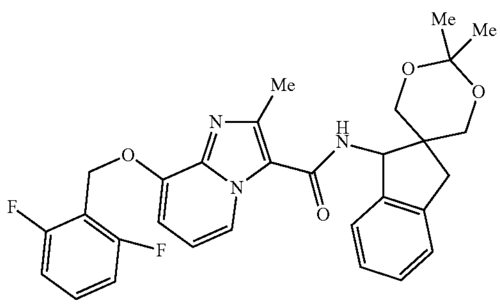
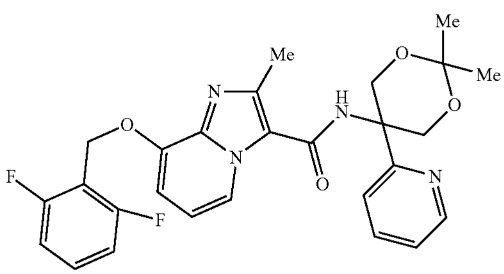
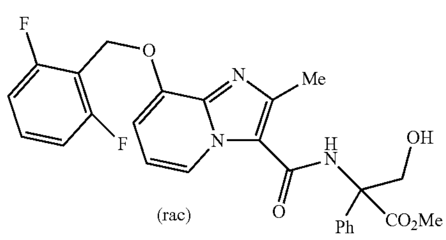
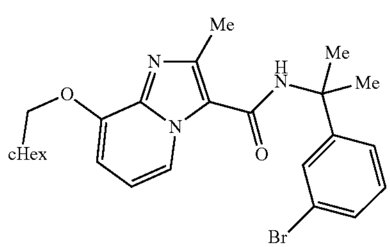
837	
838	
839	
840	
841	
842	

TABLE 96-continued

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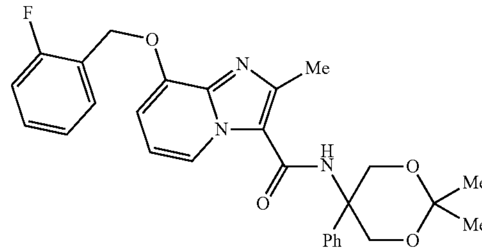
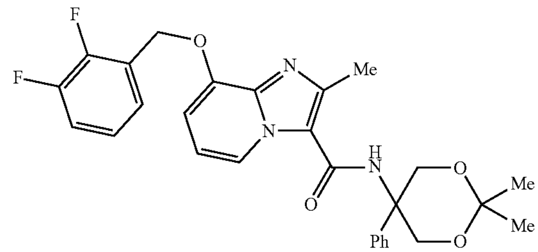
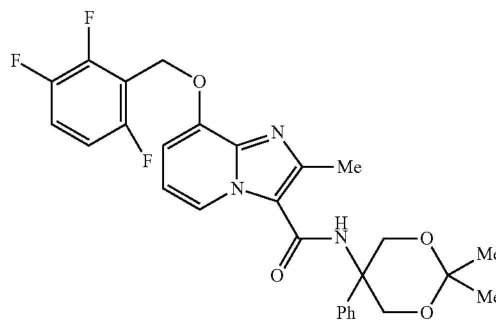
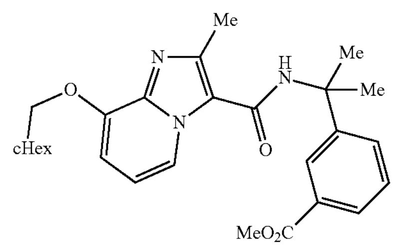
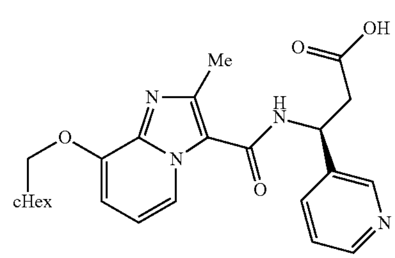
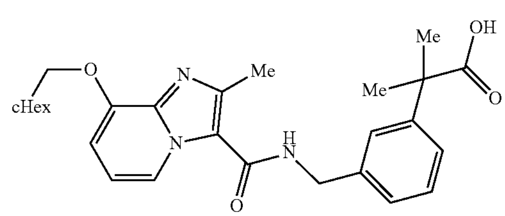
843	
844	
845	
846	
847	
848	

TABLE 97

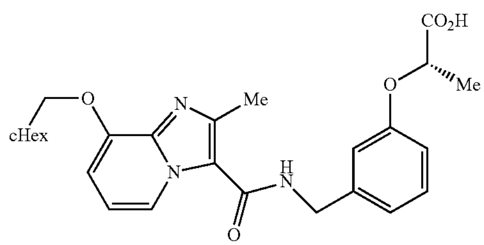
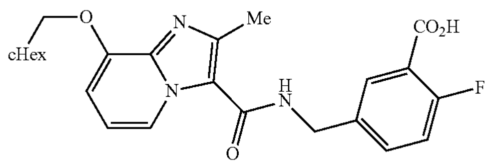
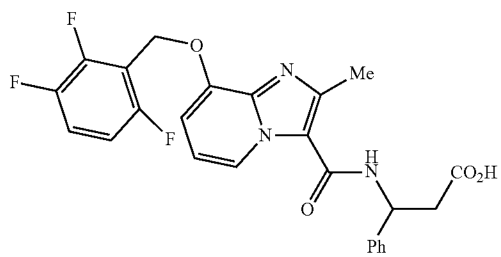
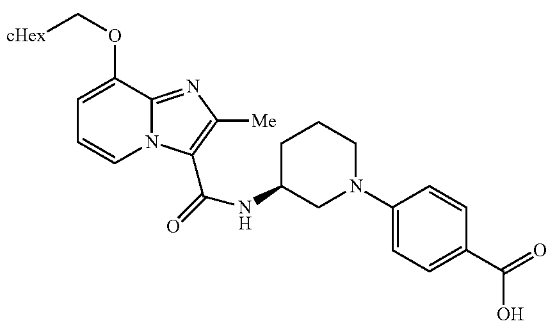
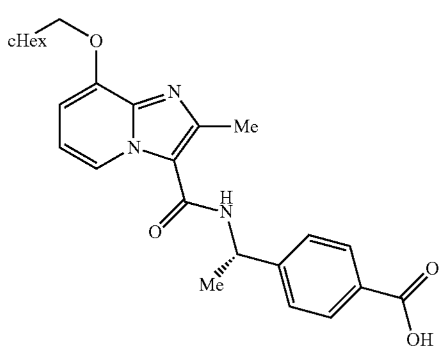
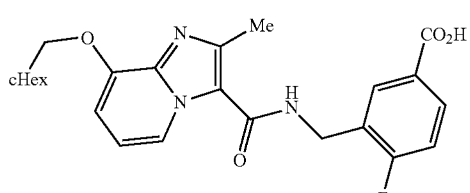
Ex	Str
849	
850	
851	
852	
853	
854	

TABLE 97-continued

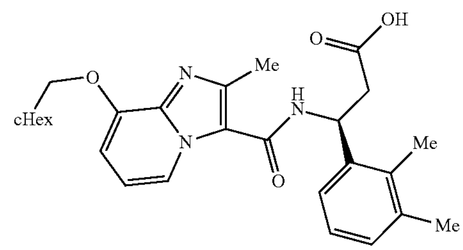
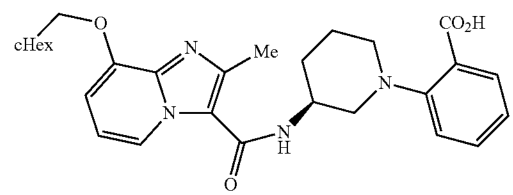
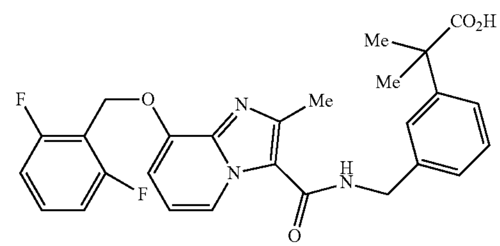
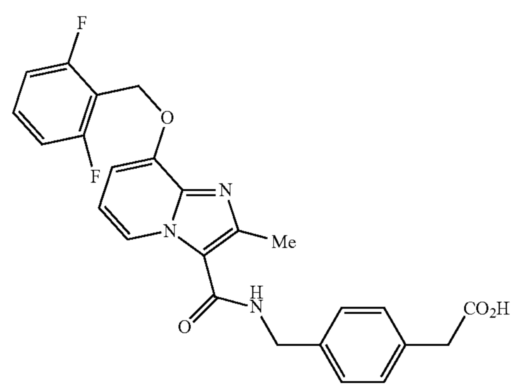
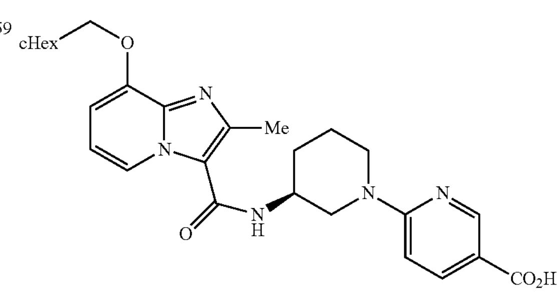
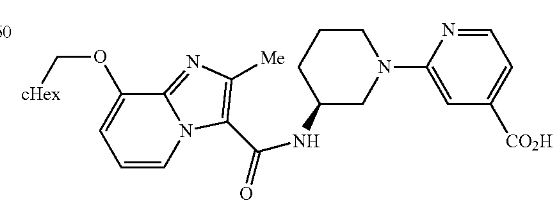
Ex	Str
855	
856	
857	
858	
859	
860	

TABLE 98

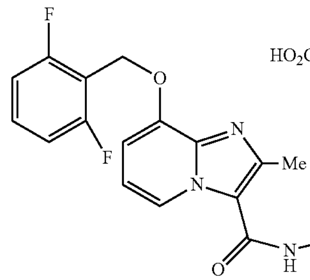
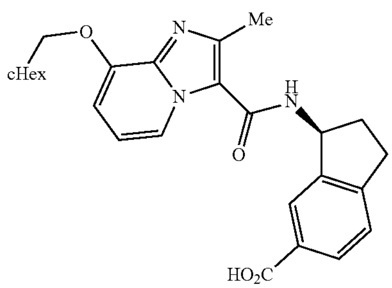
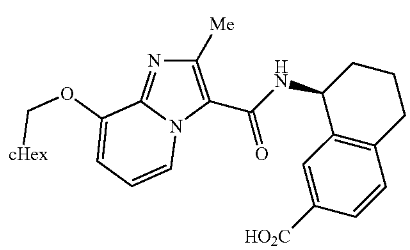
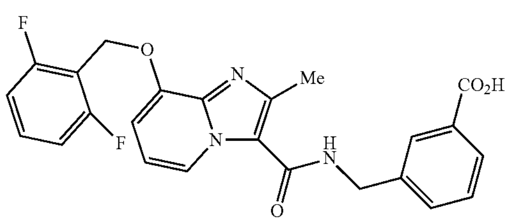
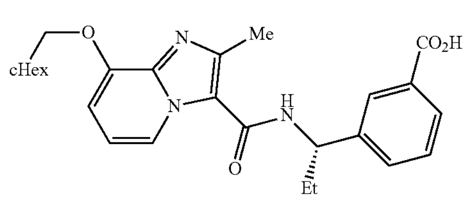
Ex	Str
861	
862	
863	
864	
865	

TABLE 98-continued

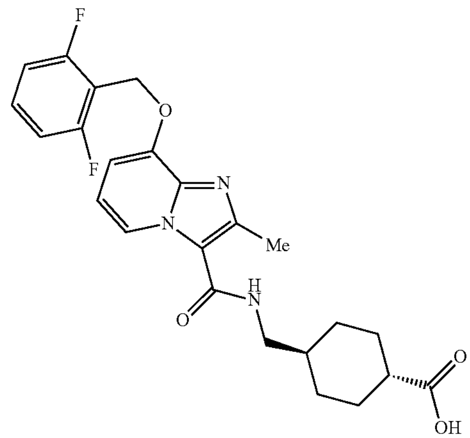
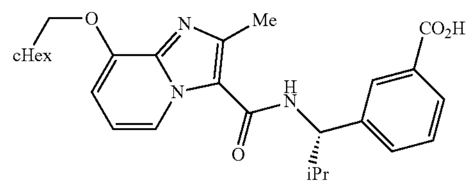
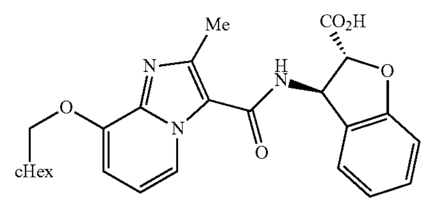
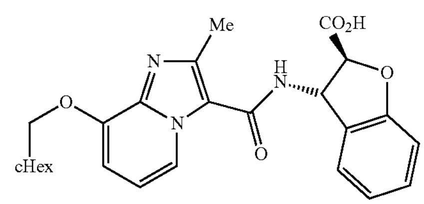
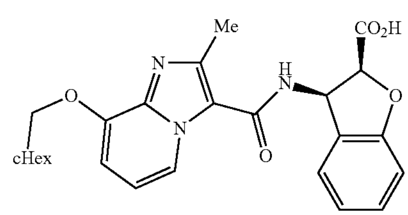
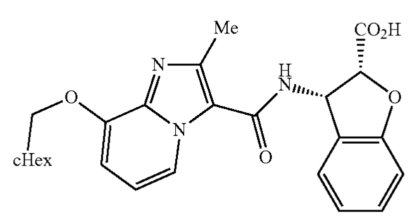
Ex	Str
866	
867	
868	
869	
870 871	 or 

TABLE 98-continued

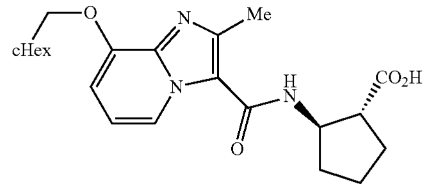
Ex	Str
872	

TABLE 99

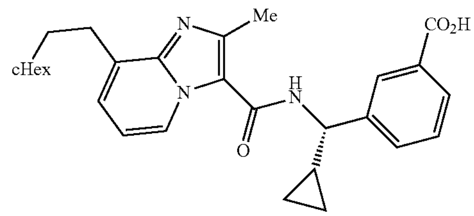
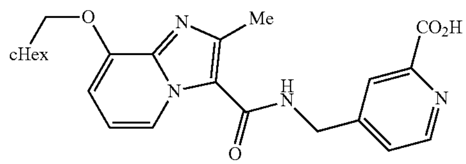
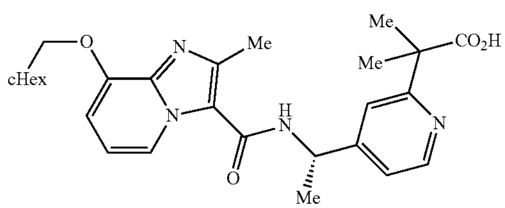
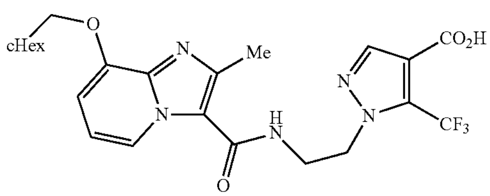
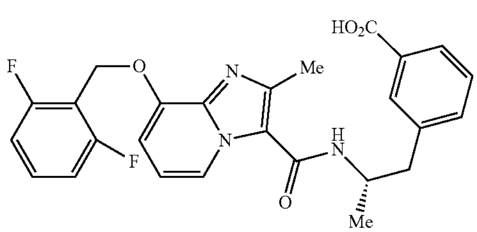
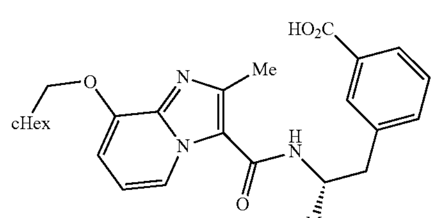
Ex	Str
873	
874	
875	
876	
877	
878	

TABLE 99-continued

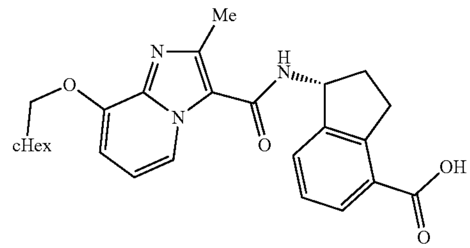
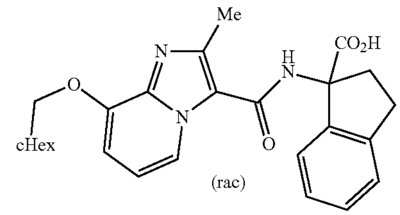
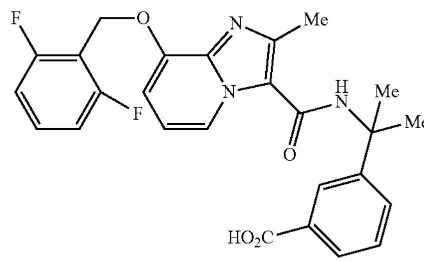
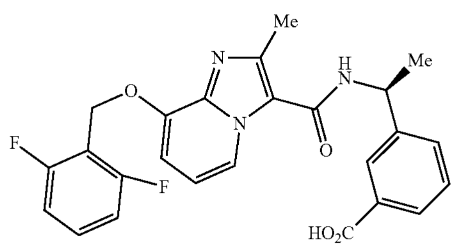
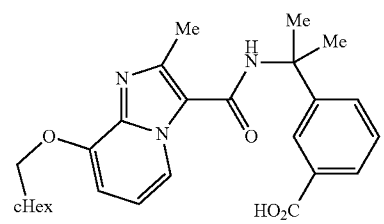
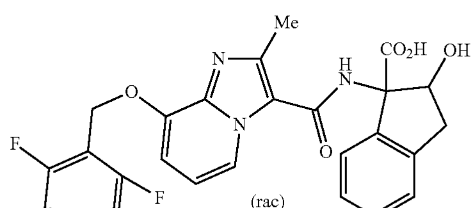
Ex	Str
879	
880	
881	
882	
883	
884	

TABLE 99-continued

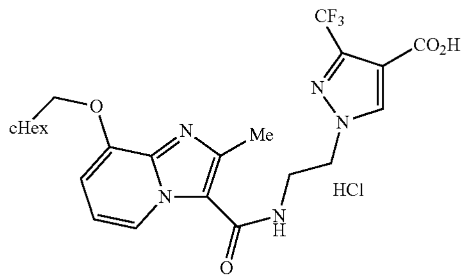
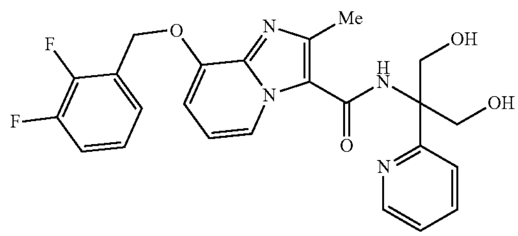
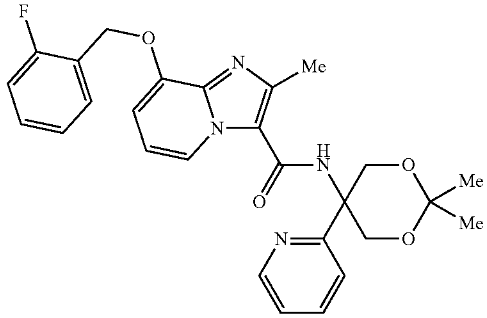
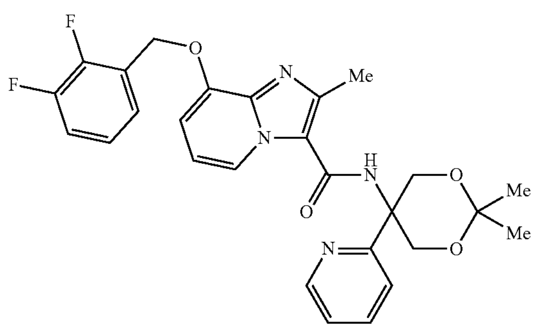
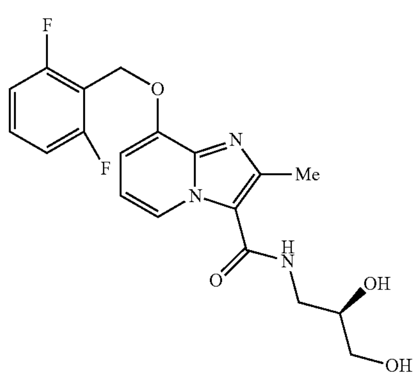
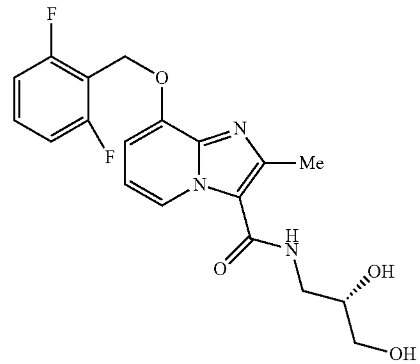
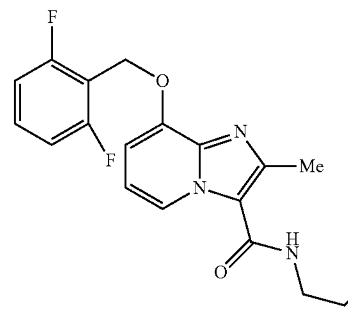
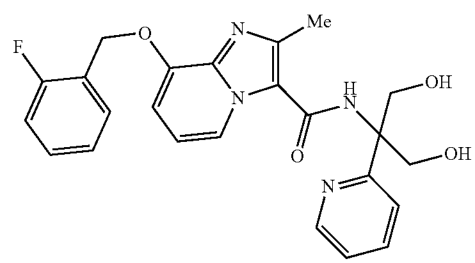
Ex	Str
885	
886	
887	
888	
889	
890	
891	
892	

TABLE 100

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4	Ex4	ESI+: 433
5	Ex5	ESI+: 371
6	Ex6	ESI+: 371
7	Ex7	ESI+: 457
8	Ex8	ESI+: 485
9	Ex9	ESI+: 521
10	Ex10	ESI+: 414
11	Ex11	ESI+: 450
12	Ex12	NMR(DMSO-d_6): 0.91 (3H, d, J = 6.6 Hz), 0.93 (3H, d, J = 6.5 Hz), 1.01-1.36 (6H, m), 1.53-1.90 (8H, m), 2.43-2.56 (2H, m), 2.51 (3H, s), 3.95 (2H, d, J = 6.1 Hz), 4.37-4.48 (1H, m), 6.77 (1H, d, J = 7.0 Hz), 6.85 (1H, t, J = 7.2 Hz), 7.71 (1H, d, J = 9.0 Hz), 8.46 (1H, d, J = 6.1 Hz), 12.22 (1H, s); ESI+: 416
13	Ex13	ESI+: 454
14	Ex14	ESI+: 436
15	Ex15	ESI+: 464
16	Ex16	ESI+: 371
17	Ex17	ESI+: 606
18	Ex18	ESI+: 450
19	Ex19	ESI+: 407
20	Ex20	ESI+: 443

TABLE 100-continued

Ex	Syn	Dat
21	Ex21	ESI+: 452
22	Ex22	ESI+: 410
23	Ex23	ESI+: 328
24	Ex24	ESI+: 422
25	Ex25	ESI+: 450
26	Ex26	ESI+: 438
27	Ex27	ESI+: 411
28	Ex28	ESI+: 421
29	Ex29	ESI+: 401
30	Ex30	ESI+: 506

TABLE 101

Ex	Syn	Dat
31	Ex31	ESI+: 534
32	Ex32	ESI+: 441
33	Ex33	ESI+: 475
34	Ex34	ESI+: 385
35	Ex35	ESI+: 513
36	Ex1	ESI+: 462
37	Ex1	ESI+: 504
38	Ex1	ESI+: 402
39	Ex1	ESI+: 416
40	Ex1	ESI+: 374
41	Ex1	ESI+: 388
42	Ex1	ESI+: 402
43	Ex1	ESI+: 402
44	Ex1	ESI+: 456
45	Ex1	ESI+: 516
46	Ex1	ESI+: 480
47	Ex1	ESI+: 472
48	Ex1	ESI+: 437
49	Ex1	ESI+: 451
50	Ex1	ESI+: 457
51	Ex1	ESI+: 471
52	Ex1	ESI+: 450
53	Ex1	ESI+: 374
54	Ex1	ESI+: 486
55	Ex1	ESI+: 442
56	Ex1	ESI+: 430
57	Ex1	ESI+: 456, 458
58	Ex1	ESI+: 431
59	Ex1	ESI+: 464
60	Ex1	ESI+: 456, 458

TABLE 102

Ex	Syn	Dat
61	Ex1	ESI+: 577
62	Ex1	ESI+: 518
63	Ex1	ESI+: 456, 458
64	Ex1	ESI+: 458
65	Ex1	ESI+: 472
66	Ex1	ESI+: 457
67	Ex1	ESI+: 440
68	Ex1	ESI+: 440
69	Ex1	ESI+: 440
70	Ex1	ESI+: 498
71	Ex1	ESI+: 415
72	Ex1	ESI+: 484
73	Ex1	ESI+: 537
74	Ex1	ESI+: 458
75	Ex1	ESI+: 428
76	Ex1	ESI+: 543
77	Ex1	ESI+: 484
78	Ex1	ESI+: 414
79	Ex1	ESI+: 499
80	Ex1	ESI+: 464
81	Ex1	ESI+: 456
82	Ex1	ESI+: 456
83	Ex1	ESI+: 486

TABLE 102-continued

Ex	Syn	Dat
84	Ex1	ESI+: 456
85	PEx11, Ex1	ESI+: 472
86	Ex1	ESI+: 471
87	Ex1	ESI+: 498
88	Ex1	ESI+: 515
89	Ex1	ESI+: 487
90	Ex1	ESI+: 357

TABLE 103

Ex	Syn	Dat
91	Ex1	ESI+: 512
92	Ex1	ESI+: 498
93	Ex1	ESI+: 484
94	Ex1	ESI+: 606
95	Ex1	ESI+: 473
96	Ex1, 16	ESI+: 360
97	Ex1, 16	ESI+: 374
98	Ex1, 16	ESI+: 409
99	Ex1, 16	ESI+: 409
100	Ex1, 16	ESI+: 409
101	Ex1, 16	ESI+: 435
102	Ex1, 16	ESI+: 408
103	Ex1, 16	ESI+: 360
104	Ex1, 16	ESI+: 342
105	Ex1, 16	ESI+: 401
106	Ex1, 16	ESI+: 386
107	Ex1, 16	ESI+: 422
108	Ex1, 16	ESI+: 462
109	Ex1, 16	ESI+: 374
110	Ex1, 16	ESI+: 388
111	Ex1, 16	ESI+: 422
112	Ex1, 16	ESI+: 360
113	Ex1, 16	ESI+: 346
114	Ex1, 16	ESI+: 388
115	Ex1, 16	ESI+: 420
116	Ex1, 16	ESI+: 332
117	Ex1, 16	ESI+: 346
118	Ex1, 16	ESI+: 388
119	Ex1, 16	ESI+: 438
120	Ex1, 16	ESI+: 461

TABLE 104

Ex	Syn	Dat
121	Ex1, 16	ESI+: 374
122	Ex1, 16	ESI+: 394
123	Ex1, 16	ESI+: 440
124	Ex1, 16	ESI+: 440
125	Ex1, 16	ESI+: 440
126	Ex1, 16	NMR(DMSO-d_6): 1.05-1.36 (5H, m), 1.63-1.79 (3H, m), 1.82-1.95 (3H, m), 2.66 (3H, s), 3.53-3.63 (4H, m), 3.97-4.07 (1H, m), 4.11 (2H, d, J = 6.1 Hz), 7.37 (1H, t, J = 7.3 Hz), 7.44 (1H, d, J = 7.9 Hz), 8.29 (1H, d, J = 6.7 Hz), 8.63 (1H, d, J = 6.5 Hz); ESI+: 362
127	Ex1, 16	ESI+: 406
128	Ex1, 16	ESI+: 406
129	Ex1, 16	ESI+: 436
130	Ex1, 16	ESI+: 394
131	Ex1, 16	ESI+: 395
132	Ex1, 16	ESI+: 422
133	Ex1, 16	ESI+: 456, 458
134	Ex1, 16	ESI+: 452
135	Ex1, 16	ESI+: 318
136	Ex1, 16	ESI+: 450
137	Ex1, 16	ESI+: 420
138	Ex1, 16	ESI+: 420
139	Ex1, 16	ESI+: 420
140	Ex1, 16	ESI+: 420
141	Ex1, 16	ESI+: 359
142	Ex1, 16	ESI+: 376

TABLE 104-continued

Ex	Syn	Dat
143	Ex1, 16	ESI+: 376
144	Ex1, 16	ESI+: 442, 444
145	Ex1, 16	ESI+: 440
146	Ex1, 16	ESI+: 440
147	Ex1, 16	ESI+: 441
148	Ex1, 16	ESI+: 362
149	Ex1, 16	ESI+: 362
150	Ex1, 16	ESI+: 442, 444

TABLE 105

Ex	Syn	Dat
151	Ex1, 16	ESI+: 414
152	Ex1, 16	ESI+: 429
153	Ex1, 16	ESI+: 376
154	Ex1, 16	ESI+: 426
155	Ex1, 16	ESI+: 426
156	Ex1, 16	ESI+: 438
157	Ex1, 16	ESI+: 438
158	Ex1, 16	ESI+: 438
159	Ex1, 16	ESI+: 390
160	Ex1, 16	ESI+: 394
161	Ex1, 16	ESI+: 392
162	Ex1, 16	ESI+: 414
163	Ex1, 16	ESI+: 398
164	Ex1, 16	ESI+ 398
165	Ex1, 16	ESI+: 399
166	Ex1, 16	ESI+: 372
167	Ex1, 16	ESI+: 386
168	Ex1, 16	ESI+: 422
169	Ex1, 16	ESI+: 434
170	Ex1, 16	ESI+: 415
171	Ex12	ESI+: 442
172	Ex12	ESI+: 402
173	Ex12	ESI+: 416
174	Ex12	ESI+: 428
175	Ex12	ESI+: 428
176	Ex12	ESI+: 416
177	Ex12	ESI+: 430
178	Ex12	ESI+: 442
179	Ex12	ESI+: 428
180	Ex12	ESI+: 442

TABLE 106

Ex	Syn	Dat
181	Ex12, 16	ESI+: 374
182	Ex13	ESI+: 470, 472
183	Ex13	ESI+: 470, 472
184	Ex13	ESI+: 470, 472
185	Ex13	ESI+: 454
186	Ex13	ESI+: 454
187	Ex16	ESI+: 464
188	Ex16	ESI+: 402
189	Ex16	ESI+: 462
190	Ex2	ESI+: 558
191	Ex2	ESI+: 522
192	Ex2	ESI+: 510
193	Ex2	ESI+: 562
194	Ex2	ESI+: 536
195	Ex2	ESI+: 550
196	Ex2	ESI+: 540
197	Ex2	ESI+: 540
198	Ex2	ESI+: 556, 558
199	Ex2	ESI+: 572
200	Ex3	ESI+: 426
201	Ex3, 16	ESI+: 458
202	Ex3, 16	ESI+: 444
203	Ex3, 16	ESI+: 408
204	Ex3, 16	ESI+: 394
205	Ex3, 16	ESI+: 396

TABLE 106-continued

Ex	Syn	Dat
206	Ex3, 16	ESI+: 448
207	Ex3, 16	ESI+: 422
208	Ex3, 16	ESI+: 436
209	Ex3, 16	ESI+: 426
210	Ex3, 16	ESI+: 442, 444

TABLE 107

Ex	Syn	Dat
211	Ex5	ESI+: 371
212	Ex5	ESI+: 357
213	Ex5	ESI+: 331
214	Ex5	ESI+: 357
215	Ex5	ESI+: 443
216	Ex5	ESI+: 399
217	Ex5	ESI+: 371
218	Ex5	ESI+: 415
219	Ex5	ESI+: 387
220	Ex5	ESI+: 373
221	Ex6	ESI+: 457
222	Ex6	ESI+: 457
223	Ex6	ESI+: 429
224	Ex6	ESI+: 387
225	Ex6, 16	ESI+: 401
226	Ex6, 16	ESI+: 385
227	Ex6, 16	ESI+: 385
228	Ex6, 16	ESI+: 371
229	Ex6, 16	ESI+: 415
230	Ex6, 16	ESI+: 413
231	Ex7, 16	ESI+: 399
232	Ex8	ESI+: 462
233	Ex8	ESI+: 485
234	Ex8, 16	ESI+: 413
235	Ex8, 16	ESI+: 399
236	Ex8, 16	ESI+: 413
237	Ex9	ESI+: 521
238	Ex9, 16	ESI+: 449
239	PEx1, Ex3, 16	ESI+: 382
240	PEx1, Ex3, 16	ESI+: 396

TABLE 108

Ex	Syn	Dat
241	PEx1, Ex3, 16	ESI+: 396
242	PEx1, Ex3, 16	ESI+: 394
243	PEx1, Ex3, 16	ESI+: 396
244	PEx1, Ex3, 16	ESI+: 456
245	PEx1, Ex3, 16	ESI+: 456
246	PEx12, Ex8	ESI+: 450
247	Ex1	ESI+: 480
248	PEx5	ESI+: 422
249	PEx5	ESI+: 436
250	PEx5	ESI+: 422
251	PEx5	NMR(DMSO-d_6): 1.01-1.34 (5H, m), 1.63-1.77 (3H, m), 1.77-1.90 (3H, m), 2.55 (3H, s), 2.82 (1H, dd, J = 5.9, 15.7 Hz), 2.91 (1H, dd, J = 8.7, 15.7 Hz), 3.95 (2H, d, J = 6.2 Hz), 5.41-5.49 (1H, m), 6.77 (1H, dd, J = 0.9, 7.8 Hz), 6.84 (1H, dd, J = 6.9, 7.6 Hz), 7.25 (1H, t, J = 7.3 Hz), 7.35 (2H, t, J = 7.6 Hz), 7.45 (2H, d, J = 7.3 Hz), 8.38 (1H, d, J = 8.4 Hz), 8.43 (1H, dd, J = 0.9, 6.8 Hz), 12.39 (1H, s); ESI+: 436
252	PEx5	ESI+: 448
253	PEx5	ESI+: 450
254	PEx5	ESI+: 490
255	PEx5	ESI+: 388
256	PEx5	ESI+: 346
257	PEx5	ESI+: 360
258	PEx5	ESI+: 374
259	PEx5	ESI+: 388
260	PEx5	ESI+: 442

TABLE 108-continued

Ex	Syn	Dat
261	PEx5	ESI+: 466
262	PEx5	ESI+: 429
263	PEx5	ESI+: 360
264	PEx5	ESI+: 428
265	PEx5	ESI+: 464
266	PEx5	ESI+: 504
267	PEx5	ESI+: 563
268	PEx5	ESI+: 429
269	PEx5	ESI+: 507
270	PEx5	ESI+: 471

TABLE 109

Ex	Syn	Dat
271	PEx5	ESI+: 443
272	PEx5	ESI+: 430
273	PEx5	ESI+: 414
274	PEx5	ESI+: 400
275	PEx5	ESI+: 450
276	PEx5	ESI+: 429
277	PEx5	ESI+: 442
278	PEx5	ESI+: 442
279	PEx5	ESI+: 507
280	PEx5	ESI+: 471
281	PEx5	ESI+: 443
282	PEx5	ESI+: 442
283	PEx5	ESI+: 401
284	PEx5	ESI+: 415
285	PEx5, Ex16	ESI+: 423
286	PEx5, Ex16	ESI+: 423
287	PEx5, Ex16	ESI+: 436
288	PEx5, Ex16	ESI+: 450
289	PEx5, Ex16	ESI+: 434
290	Ex 6	ESI+: 519
291	PEx5	ESI+: 505
292	Ex1, 16	ESI+: 477
293	Ex1	ESI+: 440
294	PEx5	ESI+: 412
295	Ex1	ESI+: 413, 415
296	Ex1	ESI+: 288
297	Ex1	ESI+: 413
298	Ex31, 16	ESI+: 534.5
299	Ex3, 16	ESI+: 404
300	Ex1	ESI+: 547
301	Ex1	ESI+: 464
302	PEx5	ESI+: 450
303	Ex3, 16	ESI+: 404
304	Ex3, 16	ESI+: 421

TABLE 110

Ex	Syn	Dat
305	PEx1	ESI+: 508
306	PEx5	ESI+: 480
307	Ex3, 16	ESI+: 404
308	PEx5	ESI+: 519
309	PEx5	ESI+: 506
310	Ex 1	ESI+: 547
311	PEx5	ESI+: 519
312	Ex1	ESI+: 471
313	PEx 5	ESI+: 443
314	Ex1	ESI+: 408
315	PEx5	ESI+: 506
316	PEx12, Ex8	ESI+: 318
317	PEx12, Ex8	ESI+: 332
318	Ex6	ESI+: 471
319	PEx5	ESI+: 443
320	Ex1	ESI+: 504
321	Ex12	NMR(DMSO-d_6): 1.01-1.36 (5H, m), 1.62-1.77 (3H, m), 1.78-1.91 (3H, m), 2.55 (3H, s), 3.10 (1H, dd, J = 9.0, 15.3 Hz), 3.22-3.37 (2H, m), 3.96 (2H,

TABLE 110-continued

Ex	Syn	Dat
		d, J = 6.2 Hz), 5.79 (1H, t, J = 8.5 Hz), 6.80 (1H, d, J = 7.1 Hz), 6.90 (1H, t, J = 7.3 Hz), 7.21-7.32 (4H, m), 8.43 (1H, d, J = 8.7 Hz), 8.55 (1H, d, J = 6.1 Hz), 12.00-12.80 (1H, br); ESI+: 448
322	Ex1	ESI+: 450
323	PEx5	NMR(DMSO-d_6): 1.01-1.34 (5H, m), 1.53 (3H, d, J = 7.0 Hz), 1.63-1.77 (3H, m), 1.78-1.90 (3H, m), 2.58 (3H, s), 3.95 (2H, d, J = 6.1 Hz), 5.18-5.27 (1H, m), 6.77 (1H, d, J = 7.2 Hz), 6.83 (1H, t, J = 7.2 Hz), 7.48 (1H, t, J = 7.7 Hz), 7.69 (1H, d, J = 7.8 Hz), 7.83 (1H, d, J = 7.7 Hz), 8.05 (1H, s), 8.41 (2H, d, J = 6.7 Hz), 12.93 (1H, s); ESI+: 436
324	PEx5	ESI+: 422
325	Ex1	ESI+: 502
326	Ex1	ESI+: 484
327	Ex9	ESI+: 521
328	Ex1	ESI+: 470
329	Ex1	ESI+: 520
330	Ex1	ESI+: 470

TABLE 111

Ex	Syn	Dat
331	Ex1	ESI+: 520
332	Ex1	ESI+: 508
333	Ex1	ESI+: 450
334	Ex1	ESI+: 506
335	Ex1	ESI+: 466
336	Ex1	ESI+: 528
337	Ex1	ESI+: 478
338	Ex1	ESI+: 432
339	Ex1	ESI+: 432
340	Ex1	ESI+: 390
341	Ex6, 16	ESI+: 371
342	Ex1, 16	ESI+: 362
343	Ex1, 16	ESI+: 441
344	Ex19	ESI+: 407
345	Ex1	ESI+: 472
346	Ex1	ESI+: 456
347	PEx15	ESI+: 303
348	Ex12	ESI+: 456
349	Ex6	ESI+: 385
350	Ex1	ESI+: 376
351	Ex1	ESI+: 438
352	Ex1	ESI+: 442
353	PEx5	ESI+: 428
354	Ex1, 16	ESI+: 411
355	Ex11	ESI+: 450
356	Ex11	ESI+: 436
357	Ex1	ESI+: 473
358	Ex5	ESI+: 373
359	Ex6, 16	ESI+: 387
360	Ex1	ESI+: 406

TABLE 112

Ex	Syn	Dat
361	Ex1	ESI+: 515
362	Ex5	ESI+: 415
363	PEx5	ESI+: 401
364	Ex6	ESI+: 429
365	Ex1, 16	ESI+: 413
366	Ex6, 16	ESI+: 413
367	Ex9, 16	ESI+: 475
368	PEx5	ESI+: 415
369	Ex1	ESI+: 436
370	Ex13	ESI+: 450
371	Ex11	ESI+: 436
372	Ex1, 16	ESI+: 415
373	Ex1, 16	ESI+: 397

TABLE 112-continued

Ex	Syn	Dat
374	Ex27, 16	ESI+: 397
375	PEx5	ESI+: 493
376	Ex9, 16	ESI+: 449
377	Ex1	ESI+: 473
378	Ex5	ESI+: 373
379	Ex6	ESI+: 387
380	Ex1	ESI+: 473
381	Ex5	ESI+: 373
382	Ex6	ESI+: 387
383	Ex1, 16	ESI+: 430
384	Ex1, 16	ESI+: 413
385	Ex12	ESI+: 446
386	Ex12	ESI+: 428
387	Ex1	ESI+: 471
388	Ex5	ESI+: 371
389	Ex12	ESI+: 414
390	Ex27, 16	ESI+: 397

TABLE 113

Ex	Syn	Dat
391	Ex9, 16	ESI+: 435
392	Ex12	ESI+: 464
393	Ex9, 16	ESI+: 449
394	Ex8, 16	ESI+: 413
395	Ex6	ESI+: 385
396	Ex1	ESI+: 529
397	Ex5	ESI+: 429
398	PEx5	ESI+: 401
399	Ex9, 16	ESI+: 435
400	Ex12	ESI+: 414
401	Ex6	ESI+: 443
402	PEx5	ESI+: 415
403	Ex1	ESI+: 436
404	Ex6, 16	ESI+: 425
405	Ex6, 16	ESI+: 468
406	Ex9, 16	ESI+: 511
407	Ex1, 16	ESI+: 415
408	Ex1, 16	ESI+: 397
409	PEx11, Ex1	ESI+: 446
410	PEx5	ESI−: 418
411	Ex1	ESI+: 506
412	Ex12	ESI+: 464
413	Ex12	ESI+: 450
414	Ex1	ESI+: 436
415	Ex1	ESI+: 436
416	Ex1	ESI+: 436
417	Ex1	ESI+: 450
418	Ex12	ESI+: 452
419	PEx5	ESI+: 436
420	Ex1, 16	ESI+: 438

TABLE 114

Ex	Syn	Dat
421	Ex12	ESI+: 450
422	Ex1, 16	ESI+: 426
423	Ex1, 16	ESI+: 456
424	Ex1, 16	ESI+: 468 NMR(DMSO-d_6): 2.70 (3H, s), 3.99 (4H, s), 5.45 (2H, s), 7.19-7.37 (6H, m), 7.39-7.43 (2H, m), 7.45-7.66 (2H, m), 7.85-8.10 (1H, m), 8.65 (1H, d, J = 6.9 Hz)
425	PEx5	ESI+: 418
426	PEx5	ESI+: 418
427	Ex12	ESI+: 472
428	PEx5	ESI+: 452
429	PEx5	ESI+: 450
430	Ex1, 16	ESI+: 450 NMR(DMSO-d_6): 2.63 (3H, s), 2.79 (1H, dd, J = 7.9, 15.5 Hz), 3.19 (1H, dd, J = 7.3, 15.5 Hz), 4.40-4.50 (1H, m), 5.33 (1H, t, J = 7.8 Hz), 5.47 (2H, s), 7.18-7.30 (6H, m), 7.37-7.50 (1H, m), 7.55-7.70 (2H, m), 8.79 (1H, d, J = 6.7 Hz), 8.84-8.96 (1H, m)
431	Ex1, 16	ESI+: 450
432	Ex1, 16	ESI+: 450
433	Ex1	ESI+: 534
434	Ex12	ESI+: 478
435	Ex1, 16	ESI+: 444
436	Ex1, 16	ESI+: 456
437	Ex6, 16	ESI+: 399
438	Ex9, 16	ESI+: 478
439	Ex1, 16	ESI+: 346
440	Ex1	ESI+: 478
441	Ex1	ESI+: 476
442	Ex1	ESI+: 302
443	PEx5	ESI+: 450
444	PEx5	ESI+: 448
445	Ex9, 16	ESI+: 464
446	Ex6	ESI+: 519
447	PEx5	ESI+: 464
448	Ex1	ESI+: 478
449	Ex1	ESI+: 492
450	Ex1	ESI+: 484

TABLE 115

Ex	Syn	Dat
451	PEx5	ESI+: 505
452	PEx5	ESI+: 470
453	PEx5	ESI+: 464
454	Ex1	ESI+: 442
455	PEx5	ESI+: 428
456	Ex1	ESI+: 506
457	Ex12	ESI+: 450
458	Ex1	ESI+: 408
459	Ex6	ESI+: 519
460	PEx1, Ex3, 16	ESI+: 444
461	PEx5	ESI+: 505
462	Ex1	ESI+: 480
463	Ex1	ESI+: 394
464	Ex1	ESI+: 427
465	Ex1	ESI+: 441
466	PEx5	ESI+: 413
467	PEx5	ESI+: 466
468	PEx5	ESI+: 413
469	PEx1	ESI+: 480
470	PEx5	ESI+: 452
471	PEx1	ESI+: 494
472	PEx5	ESI+: 466
473	Ex23	ESI+: 330
474	Ex23	ESI+: 344
475	Ex23	ESI+: 330
476	Ex23	ESI+: 344
477	Ex1	ESI+: 505
478	Ex23	ESI+: 342
479	Ex23	ESI+: 356
480	Ex23	ESI+: 370

TABLE 116

Ex	Syn	Dat
481	Ex23	ESI+: 384
482	Ex23	ESI+: 358
483	Ex23	ESI+: 408
484	Ex23	ESI+: 360
485	Ex23	ESI+: 438
486	Ex23	ESI+: 376
487	Ex23	ESI+: 374
488	Ex23	ESI+: 412
489	Ex23	ESI+: 412
490	Ex23	ESI+: 386
491	Ex23	ESI+: 346

TABLE 116-continued

Ex	Syn	Dat
492	Ex23	ESI+: 360
493	Ex23	ESI+: 360
494	Ex23	ESI+: 372
495	Ex23	ESI+: 400
496	Ex23	ESI+: 420
497	Ex23	ESI+: 359
498	Ex23	ESI+: 387
499	Ex23	ESI+: 373
500	Ex23	ESI+: 401
501	Ex23	ESI+: 399
502	Ex23	ESI+: 399
503	Ex23	ESI+: 385
504	Ex23	ESI+: 399
505	Ex23	ESI+: 399
506	Ex23	ESI+: 415
507	Ex23	ESI+: 413
508	Ex23	ESI+: 399
509	Ex23	ESI+: 397
510	Ex23	ESI+: 397

TABLE 117

Ex	Syn	Dat
511	Ex23	ESI+: 428
512	Ex23	ESI+: 414
513	Ex23	ESI+: 413
514	Ex23	ESI+: 399
515	Ex23	ESI+: 413
516	Ex23	ESI+: 399
517	Ex23	ESI+: 399
518	Ex23	ESI+: 449
519	Ex23	ESI+: 463
520	Ex23	ESI+: 379
521	Ex23	ESI+: 379
522	Ex23	ESI+: 379
523	Ex23	ESI+: 393
524	Ex23	ESI+: 393
525	Ex23	ESI+: 393
526	Ex23	ESI+: 407
527	Ex23	ESI+: 407
528	Ex23	ESI+: 378
529	Ex23	ESI+: 392
530	Ex23	ESI+: 392
531	Ex23	ESI+: 392
532	Ex23	ESI+: 396
533	Ex23	ESI+: 396
534	Ex23	ESI+: 392
535	Ex23	ESI+: 406
536	Ex23	ESI+: 406
537	Ex23	ESI+: 410
538	Ex23	ESI+: 454
539	Ex23	ESI+: 406
540	Ex23	ESI+: 408

TABLE 118

Ex	Syn	Dat
541	Ex23	ESI+: 408
542	Ex23	ESI+: 422
543	Ex23	ESI+: 422
544	Ex23	ESI+: 463
545	Ex23	ESI+: 408
546	Ex23	ESI+: 447
547	Ex23	ESI+: 447
548	Ex23	ESI+: 461
549	Ex23	ESI+: 465
550	Ex23	ESI+: 372
551	Ex23	ESI+: 386
552	Ex23	ESI+: 386
553	Ex23	ESI+: 386
554	Ex23	ESI+: 400

TABLE 118-continued

Ex	Syn	Dat
555	Ex23	ESI+: 433
556	Ex23	ESI+: 408
557	Ex23	ESI+: 413
558	Ex23	ESI+: 375
559	Ex26	ESI+: 422
560	Ex26	ESI+: 380
561	Ex26	ESI+: 382
562	Ex26	ESI+: 368
563	Ex26	ESI+: 410
564	Ex26	ESI+: 480, 482
565	Ex26	ESI+: 416
566	Ex26	ESI+: 436, 438
567	Ex26	ESI+: 427
568	PEx5	ESI+: 491
569	Ex26	ESI+: 438
570	Ex26	ESI+: 454, 456

TABLE 119

Ex	Syn	Dat
571	Ex26	ESI+: 434
572	Ex26	ESI+: 438
573	Ex26	ESI+: 454, 456
574	Ex26	ESI+: 456
575	Ex26	ESI+: 488
576	Ex26	ESI+: 456
577	Ex26	ESI+: 420
578	Ex26	ESI+: 438
579	Ex26	ESI+: 438
580	Ex26	ESI+: 420
581	Ex26	ESI+: 416
582	Ex26	ESI+: 403
583	Ex26	ESI+: 442, 444
584	Ex26	ESI+: 444, 446
585	Ex26	ESI+: 407
586	Ex26	ESI+: 443, 445
587	Ex26	ESI+: 423
588	Ex24	ESI+: 436
589	Ex24	ESI+: 376
590	Ex1	ESI+: 506
591	Ex24	ESI+: 438
592	Ex24	ESI+: 386
593	Ex24	ESI+: 402
594	Ex24	ESI+: 420
595	Ex24	ESI+: 402
596	Ex24	ESI+: 430
597	Ex24	ESI+: 500, 502
598	Ex24	ESI+: 428
599	Ex24	ESI+: 428
600	Ex24	ESI+: 400

TABLE 120

Ex	Syn	Dat
601	Ex24	ESI+: 386
602	Ex24	ESI+: 400
603	Ex24	ESI+: 402
604	Ex24	ESI+: 450
605	Ex24	ESI+: 514, 516
606	Ex24	ESI+: 480
607	Ex24	ESI+: 478
608	Ex24	ESI+: 464
609	Ex24	ESI+: 504
610	Ex24	ESI+: 481
611	Ex24	ESI+: 452
612	Ex24	ESI+: 504
613	Ex24	ESI+: 480
614	Ex24	ESI+: 514, 516
615	Ex24	ESI+: 450
616	Ex24	ESI+: 450
617	Ex24	ESI+: 464

TABLE 120-continued

Ex	Syn	Dat
618	Ex24	ESI+: 514, 516
619	Ex24	ESI+: 478
620	Ex24	ESI+: 496
621	Ex24	ESI+: 494
622	Ex24	ESI+: 464
623	Ex24	ESI+: 472
624	Ex24	ESI+: 464
625	Ex24	ESI+: 430
626	Ex24	ESI+: 414
627	Ex24	ESI+: 400
628	Ex24	ESI+: 436
629	Ex24	ESI+: 374
630	Ex24	ESI+: 428

TABLE 121

Ex	Syn	Dat
631	Ex24	ESI+: 414
632	Ex24	ESI+: 414
633	Ex24	ESI+: 422
634	Ex24	ESI+: 422
635	Ex24	ESI+: 436
636	Ex24	ESI+: 428
637	Ex24	ESI+: 436
638	Ex24	ESI+: 436
639	Ex24	ESI+: 505
640	Ex23	ESI+: 370
641	PEx5	ESI+: 492
642	Ex25	ESI+: 414
643	Ex23	ESI+: 368
644	Ex23	ESI+: 368
645	Ex23	ESI+: 412
646	Ex23	ESI+: 369
647	Ex23	ESI+: 382
648	Ex23	ESI+: 381
649	Ex23	ESI+: 399
650	Ex23	ESI+: 447
651	Ex23	ESI+: 413, 415
652	Ex23	ESI+: 410
653	Ex23	ESI+: 422
654	Ex23	ESI+: 404
655	Ex23	ESI+: 418
656	Ex1	ESI+: 450
657	Ex1,16	ESI+: 456
658	Ex1,16	ESI+: 406

TABLE 122

Ex	Syn	Dat
659	Ex1	ESI+: 476
660	Ex12	ESI+: 454
661	Ex661	ESI+: 462
662	PEx5	ESI+: 448
663	Ex663	APCI/ESI+: 476
664	PEx11, Ex1	ESI+: 480
665	Ex1	ESI+: 462
666	Ex1	ESI+: 504
667	Ex1	ESI+: 480
668	Ex1	ESI+: 476
669	Ex1	ESI+: 476
670	Ex1	APCI/ESI+: 476
671	Ex1	ESI+: 510
672	Ex1	ESI+: 480
673	Ex1	ESI+: 506
674	Ex1	ESI+: 510
675	Ex1	ESI+: 518
676	Ex1	ESI+: 474
677	Ex1	ESI+: 492
678	Ex1	ESI+: 510
679	Ex1	ESI+: 510

TABLE 122-continued

Ex	Syn	Dat
680	Ex1	ESI+: 540
681	Ex1	ESI+: 510
682	Ex1	ESI+: 540
683	Ex1	ESI+: 480
684	Ex1	ESI+: 480
685	Ex1	ESI+: 480
686	Ex12	ESI+: 448
687	Ex12	ESI+: 462
688	Ex12	ESI+: 484
689	Ex12	ESI+: 454
690	Ex12	ESI+: 484

TABLE 123

Ex	Syn	Dat
691	Ex661	ESI+: 466
692	Ex661	ESI+: 462
693	Ex661	ESI+: 462 NMR (DMSO-d_6): 1.01-1.36 (5H, m), 1.62-1.77 (3H, m), 1.77-1.90 (3H, m), 2.24 (3H, s), 2.54 (3H, s), 2.99 (1H, dd, J = 8.7, 15.6 Hz), 3.19-3.36 (2H, m), 3.96 (2H, d, J = 6.2 Hz), 5.79 (1H, t, J = 8.5 Hz), 6.80 (1H, dd, J = 0.8, 7.8 Hz), 6.89 (1H, t, J = 7.3 Hz), 7.06-7.18 (3H, m), 8.41 (1H, d, J = 8.7 Hz), 8.55 (1H, dd, J = 0.8, 6.8 Hz), 12.48 (1H, s)
694	Ex661	APCI/ESI+: 462
695	Ex661	APCI/ESI+: 462
696	Ex661	ESI+: 496
697	Ex661	EI: 466
698	Ex661	ESI+: 492 NMR (DMSO-d_6): 2.24 (3H, s), 2.51 (3H, s), 2.99 (1H, dd, J = 8.7, 15.6 Hz), 3.19-3.36 (2H, m), 5.32 (2H, s), 5.79 (1H, t, J = 8.5 Hz), 6.96 (1H, t, J = 7.2 Hz), 7.03 (1H, dd, J = 0.9, 7.8 Hz), 7.06-7.18 (3H, m), 7.19-7.27 (2H, m), 7.54-7.63 (1H, m), 8.43 (1H, d, J = 8.7 Hz), 8.61 (1H, dd, J = 0.9, 6.8 Hz), 12.48 (1H, s)
699	Ex661	ESI+: 496 NMR (DMSO-d_6): 2.47 (3H, s), 3.06-3.18 (1H, m), 3.33-3.43 (2H, m), 5.31 (2H, s), 5.97 (1H, t, J = 7.7 Hz), 6.95 (1H, t, J = 7.2 Hz), 6.99-7.06 (2H, m), 7.12 (1H, d, J = 7.5 Hz), 7.19-7.27 (2H, m), 7.32 (1H, dt, Jd = 5.2, Jt = 7.7 Hz), 7.58 (1H, tt, J = 6.7, 8.5 Hz), 8.51-8.57 (2H, m), 12.56 (1H, s)
700	Ex661	ESI+: 460
701	Ex661	ESI+: 478

TABLE 124

Ex	Syn	Dat
702	Ex661	ESI+: 496 NMR (DMSO-d_6): 2.52 (3H, s), 3.10 (1H, dd, J = 8.9, 15.3 Hz), 3.22-3.38 (2H, m), 5.37 (2H, s), 5.79 (1H, t, J = 8.5 Hz), 6.97 (1H, t, J = 7.2 Hz), 7.03 (1H, dd, J = 0.9, 7.8 Hz), 7.22-7.33 (5H, m), 7.66 (1H, dq, Jd = 5.1, Jq = 9.6 Hz), 8.47 (1H, d, J = 8.8 Hz), 8.63 (1H, dd, J = 0.9, 6.8 Hz), 12.20-12.70 (1H, br)
703	Ex661	ESI+: 466
704	Ex661	NMR (DMSO-d_6): 1.00-1.35 (5H, m), 1.62-1.77 (3H, m), 1.77-1.90 (3H, m), 2.50 (3H, s), 3.05-3.18 (1H, m), 3.32-3.43 (2H, m), 3.96 (2H, d, J = 6.2 Hz), 5.96 (1H, t, J = 7.6 Hz), 6.79 (1H, d, J = 7.6 Hz), 6.88 (1H, t, J = 7.3 Hz), 7.02 (1H, t, J = 9.0 Hz), 7.12 (1H, d, J = 7.5 Hz), 7.29-7.35 (1H, m), 8.46 (1H, d, J = 6.7 Hz), 8.52 (1H, d, J = 8.8 Hz), 12.55 (1H, s); ESI+: 466

TABLE 124-continued

Ex	Syn	Dat
705	Ex661	ESI+: 466 NMR (DMSO-d_6): 1.00-1.34 (5H, m), 1.62-1.77 (3H, m), 1.77-1.90 (3H, m), 2.50 (3H, s), 3.05-3.18 (1H, m), 3.32-3.43 (2H, m), 3.96 (2H, d, J = 6.1 Hz), 5.97 (1H, t, J = 7.7 Hz), 6.79 (1H, d, J = 7.0 Hz), 6.88 (1H, t, J = 7.3 Hz), 7.02 (1H, t, J = 9.0 Hz), 7.12 (1H, d, J = 7.5 Hz), 7.29-7.35 (1H, m), 8.46 (1H, dd, J = 0.9, 6.8 Hz), 8.52 (1H, d, J = 8.9 Hz), 12.57 (1H, s)
706	Ex661	ESI+: 466 NMR (DMSO-d_6): 1.01-1.36 (5H, m), 1.62-1.78 (3H, m), 1.78-1.91 (3H, m), 2.54 (3H, s), 3.10 (1H, dd, J = 9.1, 16.2 Hz), 3.23-3.42 (2H, m), 3.96 (2H, d, J = 6.1 Hz), 5.73 (1H, t, J = 8.4 Hz), 6.81 (1H, d, J = 7.4 Hz), 6.90 (1H, t, J = 7.3 Hz), 7.06 (1H, dt, Jd = 2.3, Jt = 8.8 Hz), 7.12 (1H, dd, J = 2.1, 9.1 Hz), 7.31 (1H, dd, J = 5.3, 8.1 Hz), 8.42 (1H, d, J = 8.6 Hz), 8.55 (1H, d, J = 6.8 Hz), 12.40-12.70 (1H, br)
707	Ex1	ESI+: 462
708	Ex1	ESI+: 492
709	Ex709	APCI/ESI+: 482
710	Ex710	ESI+: 532
711	Ex711	ESI+: 448
712	Ex712	ESI+: 480
713	Ex713	ESI+: 392
714	Ex714	ESI+: 496
715	Ex1	ESI+: 512

TABLE 125

Ex	Syn	Dat
716	Ex1	NMR ($CDCl_3$): 1.00-1.12 (2H, m), 1.15-1.38 (3H, m), 1.66-1.81 (3H, m), 1.94-2.10 (3H, m), 2.85 (3H, s), 3.04 (2H, d, J = 5.0 Hz), 3.66 (3H, s), 3.95 (2H, d, J = 6.6 Hz), 5.68-5.74 (1H, m), 6.62 (1H, d, J = 7.7 Hz), 6.77 (1H, t, J = 7.1 Hz), 7.29 (1H, dd, J = 4.9 Hz, 8.0 Hz), 7.50 (1H, d, J = 8.0 Hz), 7.71 (1H, d, J = 8.0 Hz), 8.54 (1H, d, J = 4.8 Hz), 8.67 (1H, s), 9.00 (1H, d, J = 6.8 Hz)
717	Ex1	ESI+: 478
718	Ex1	ESI+: 480
719	Ex1	ESI+: 454
720	Ex1	ESI+: 501
721	Ex1	ESI+: 409
722	Ex1	ESI+: 505
723	Ex1	ESI+: 498
724	Ex1	ESI+: 439
725	Ex1	ESI+: 450
726	Ex1	ESI+: 468
727	Ex1	ESI+: 505
728	Ex1	ESI+: 478
729	Ex1	ESI+: 508
730	Ex1	ESI+: 480
731	Ex1	ESI+: 506
732	Ex1	ESI+: 506
733	Ex1	ESI+: 508
734	Ex1	ESI+: 476
735	Ex1	ESI+: 466
736	Ex1	ESI+: 528
737	Ex1	ESI+: 478
738	Ex1	ESI+: 464
739	Ex1	ESI+: 472
740	PEx10, 11, Ex1	ESI+: 498
741	Ex1	ESI+: 464
742	Ex1	ESI+: 464

TABLE 126

Ex	Syn	Dat
743	Ex1	ESI+: 464
744	Ex1	ESI+: 464
745	Ex1	ESI+: 528
746	Ex1	ESI+: 414
747	Ex1	ESI+: 437
748	Ex1	ESI+: 476
749	Ex1	ESI+: 492
750	Ex1	ESI+: 522
751	Ex1	ESI+: 522
752	Ex1	ESI+: 464
753	Ex1	ESI+: 494
754	Ex1	ESI+: 462
755	Ex1	ESI+: 466
756	Ex1	ESI+: 466
757	Ex1	APCI/ESI+: 392
758	Ex1	ESI+: 466 NMR (DMSO-d_6): 2.55 (3H, s), 4.11 (1H, q, J = 7.2 Hz), 4.74 (1H, t, J = 6.4 Hz), 5.20 (1H, t, J = 8.4 Hz), 5.32 (2H, s), 5.58 (1H, d, J = 6.3 Hz), 5.76 (1H, d, J = 5.9 Hz), 6.96 (1H, t, J = 7.2 Hz), 7.03 (1H, dd, J = 0.9, 7.7 Hz), 7.18-7.35 (6H, m), 7.59 (1H, tt, J = 6.7, 8.4 Hz), 8.33 (1H, d, J = 8.8 Hz), 8.64 (1H, dd, J = 0.8, 6.8 Hz)
759	Ex1	ESI+: 466 NMR (DMSO-d_6): 2.53 (3H, s), 4.18 (1H, q, J = 6.4 Hz), 4.82 (1H, t, J = 5.1 Hz), 5.06 (1H, d, J = 5.1 Hz), 5.10 (1H, d, J = 6.9 Hz), 5.32 (2H, s), 5.45 (1H, t, J = 7.9 Hz), 6.96 (1H, t, J = 7.2 Hz), 7.02 (1H, dd, J = 0.9, 7.8 Hz), 7.19-7.40 (6H, m), 7.59 (1H, tt, J = 6.7, 8.5 Hz), 8.26 (1H, d, J = 8.8 Hz), 8.64 (1H, dd, J = 0.8, 6.7 Hz)
760	Ex1	ESI+: 468
761	Ex1	ESI+: 476
762	Ex1	ESI+: 496
763	Ex1	ESI+: 432

TABLE 127

Ex	Syn	Dat
764	Ex1	ESI+: 482
765	Ex1	APCI/ESI+: 509
766	Ex1	ESI+: 494 NMR (DMSO-d_6): 2.37 (4H, d, J = 5.3 Hz), 2.63 (3H, s), 4.04-4.12 (2H, m), 4.69 (2H, d, J = 4.5 Hz), 5.31 (2H, s), 6.87 (1H, t, J = 7.3 Hz), 6.98 (1H, dd, J = 0.7, 7.7 Hz), 7.17 (1H, t, J = 7.2 Hz), 7.23 (2H, t, J = 8.0 Hz), 7.30 (2H, t, J = 7.8 Hz), 7.37 (2H, dd, J = 1.2, 8.4 Hz), 7.58 (1H, tt, J = 6.7, 8.5 Hz), 8.21 (1H, s), 8.52 (1H, dd, J = 0.8, 6.9 Hz)
767	Ex1	ESI+: 494 NMR (DMSO-d_6): 2.12 (2H, dd, J = 6.0, 14.2 Hz), 2.57 (3H, s), 2.64 (2H, dd, J = 6.2, 14.2 Hz), 4.10-4.18 (2H, m), 4.62 (2H, d, J = 4.3 Hz), 5.31 (2H, s), 6.89 (1H, t, J = 7.3 Hz), 6.98 (1H, d, J = 7.0 Hz), 7.17 (1H, t, J = 7.3 Hz), 7.23 (2H, t, J = 8.0 Hz), 7.30 (2H, t, J = 7.7 Hz), 7.46 (2H, dd, J = 1.1, 8.4 Hz), 7.59 (1H, tt, J = 6.7, 8.4 Hz), 8.19 (1H, s), 8.37 (1H, dd, J = 0.8, 6.9 Hz)
768	Ex1	ESI+: 492
769	Ex1	ESI+: 462
770	Ex1	ESI+: 462
771	Ex1	ESI+: 432
772	Ex1	ESI+: 390 NMR (DMSO-d_6): 1.35 (6H, s), 2.49 (3H, s), 3.52 (2H, d, J = 5.7 Hz), 4.99 (1H, t, J = 5.7 Hz), 5.30 (2H, s), 6.91 (1H, t, J = 7.2 Hz), 6.99 (1H, dd, J = 0.9, 7.7 Hz), 7.14 (1H, s), 7.23 (2H, t, J = 8.0 Hz), 7.58 (1H, tt, J = 6.7, 8.5 Hz), 8.60 (1H, dd, J = 0.9, 6.9 Hz)
773	Ex1	ESI+: 404
774	Ex709	ESI+: 451
775	Ex1	ESI+: 418

TABLE 127-continued

Ex	Syn	Dat
776	Ex1	ESI+: 376
777	Ex1	ESI+: 390
778	Ex1	ESI+: 404

TABLE 128

Ex	Syn	Dat
779	Ex1	ESI+: 402
780	Ex1	ESI+: 494
781	Ex1	APCI/ESI+: 478
782	Ex1	ESI+: 468
783	Ex1	ESI+: 468
784	Ex1	ESI+: 480
785	Ex1	ESI+: 480
786	Ex1	ESI+: 480
787	Ex1	ESI+: 480
788	Ex1	ESI+: 508
789	Ex1	ESI+: 452
790	Ex1	ESI+: 452
791	Ex1	ESI+: 480
792	Ex1	ESI+: 508
793	Ex1	ESI+: 424
794	Ex1	ESI+: 493
795	Ex1	ESI+: 493
796	Ex1	ESI+: 439
797	Ex1	ESI+: 466 NMR (DMSO-d_6): 2.55 (3H, s), 4.15-4.22 (1H, m), 4.82 (1H, brs), 5.04-5.12 (2H, m), 5.41 (2H, s), 5.45 (1H, t, J = 7.9 Hz), 6.92-7.01 (2H, m), 7.25-7.40 (5H, m), 7.42-7.54 (2H, m), 8.27 (1H, d, J = 8.8 Hz), 8.63 (1H, dd, J = 1.0, 6.6 Hz)
798	Ex1	ESI+: 448 NMR (DMSO-d_6): 2.54 (3H, s), 4.15-4.22 (1H, m), 4.82 (1H, d, J = 5.1 Hz), 5.03-5.13 (2H, m), 5.34 (2H, s), 5.45 (1H, t, J = 7.9 Hz), 6.92-7.00 (2H, m), 7.25-7.40 (6H, m), 7.44-7.51 (1H, m), 7.63 (1H, dt, Jd = 1.7 Hz, Jt = 7.6 Hz), 8.26 (1H, d, J = 8.8 Hz), 8.62 (1H, dd, J = 1.1, 6.6 Hz)
799	Ex1,16	ESI+: 383
800	Ex1,16	ESI+: 432
801	Ex1,16	ESI+: 450
802	Ex1,16	ESI+: 450
803	Ex1,16	ESI+: 468
804	Ex1,16	ESI+: 468
805	Ex1,16	ESI+: 438
806	Ex1,16	ESI+: 456
807	Ex1,16	ESI+: 474
808	Ex1,16	ESI+: 474
808	Ex1,16	ESI+: 474
809	Ex1,16	ESI+: 468
810	Ex1.16	ESI+: 464
811	Ex1	ESI+: 462
812	Ex12	ESI+: 456

TABLE 129

Ex	Syn	Dat
813	Ex12	ESI+: 472
814	Ex12	ESI+: 442
815	Ex12	ESI+: 472
816	Ex12	ESI+: 452
817	Ex14	ESI+: 464
818	Ex16	ESI+: 466
819	Ex27,16	ESI+: 441
820	Ex31	ESI+: 438
821	Ex31, PEx5,Ex16	ESI+: 506
822	Ex5	ESI+: 401
823	Ex6	ESI+: 549
824	Ex1, PEx5	ESI+: 448
825	Ex661	ESI+: 448

TABLE 129-continued

Ex	Syn	Dat
826	Ex661	ESI+: 448
827	Ex709	APCI/ESI+: 482
828	Ex709	ESI+: 450
829	Ex709	ESI+: 468 NMR (DMSO-d_6): 2.67 (3H, s), 3.98 (4H, d, J = 5.5 Hz), 5.05 (2H, t, J = 5.5 Hz), 5.41 (2H, s), 6.90 (1H, t, J = 7.3 Hz), 6.98 (1H, dd, J = 0.8, 7.7 Hz), 7.21 (1H, tt, J = 1.2, 7.3 Hz), 7.26-7.33 (3H, m), 7.40-7.54 (5H, m), 8.62 (1H, dd, J = 0.9, 6.9 Hz)
830	Ex709	ESI+: 486
831	Ex709	APCI/ESI+: 482
832	Ex709	APCI/ESI+: 469
833	Ex709	ESI+: 494
834	Ex709	APCI/ESI+: 469 NMR (DMSO-d_6): 2.70 (3H, s), 3.99 (2H, dd, J = 6.2, 10.9 Hz), 4.21 (2H, dd, J = 5.4, 10.9 Hz), 4.94 (2H, t, J = 5.8 Hz), 5.32 (2H, s), 6.94 (1H, t, J = 7.3 Hz), 7.03 (1H, dd, J = 0.8, 7.8 Hz), 7.19-7.31 (3H, m), 7.54-7.63 (2H, m), 7.79 (1H, dt, Jd = 1.8 Hz, Jt = 7.8 Hz), 8.01 (1H, s), 8.53 (1H, ddd, J = 0.9, 1.8, 4.9 Hz), 8.76 (1H, dd, J = 0.9, 6.9 Hz)

TABLE 130

Ex	Syn	Dat
835	Ex713	ESI+: 406
836	Ex8	APCI/ESI+: 522
837	Ex8	APCI/ESI+: 522
838	Ex8	APCI/ESI+: 522
839	Ex8	ESI+: 534
840	Ex8	APCI/ESI+: 509
841	Ex8	ESI+: 496
842	Ex8	ESI+: 484
843	PEx12, Ex8	ESI+: 490
844	PEx12, Ex8	ESI+: 508
845	PEx12, Ex8	ESI+: 526
846	PEx165	ESI+: 464
847	PEx5	ESI+: 437
848	PEx5	ESI+: 464
849	PEx5	ESI+: 466
850	PEx5	ESI+: 440
851	PEx5	ESI+: 484
852	PEx5	ESI+: 491
853	PEx5	ESI+: 436
854	PEx5	ESI+: 440
855	PEx5	ESI+: 464
856	PEx5	ESI+: 491
857	PEx5	ESI+: 494
858	PEx5	ESI+: 466
859	PEx5	ESI+: 492
860	PEx5	ESI+: 492
861	PEx5	ESI+: 480
862	Ex1, PEx5	ESI+: 448
863	PEx5	ESI+: 462
864	PEx5	ESI+: 452
865	PEx5	ESI+: 450
866	PEx5	ESI+: 458
867	PEx5	ESI+: 464
868	PEx5	ESI+: 450

TABLE 131

Ex	Syn	Dat
869	PEx5	ESI+: 450
870	PEx5	ESI+: 450
871	PEx5	ESI+: 450
872	PEx5	ESI+: 400
873	PEx5	ESI+: 462
874	PEx5	ESI+: 423

TABLE 131-continued

Ex	Syn	Dat
875	PEx5	ESI+: 478
876	PEx5	ESI+: 494
877	PEx5	ESI+: 480
878	PEx5	ESI+: 450
879	PEx5	ESI+: 448
880	PEx5	ESI+: 448
881	PEx5	ESI+: 480
882	PEx5	ESI+: 466
883	PEx5	ESI+: 450 NMR (DMSO-d_6): 1.00-1.33 (5H, m), 1.62-1.90 (6H, m), 1.72 (6H, s), 2.65 (3H, s), 3.95 (2H, d, J = 6.2 Hz), 6.76 (1H, dd, J = 0.9, 7.7 Hz), 6.81 (1H, t, J = 7.1 Hz), 7.45 (1H, t, J = 7.8 Hz), 7.70 (1H, dq, Jd = 7.9 Hz, Jq = 1.0 Hz), 7.78 (1H, dt, Jd = 7.8 Hz, Jt = 1.2 Hz), 8.05 (1H, t, J = 1.7 Hz), 8.17 (1H, s), 8.32 (1H, dd, J = 0.9, 6.7 Hz), 12.70-13.00 (1H, br)
884	PEx5	ESI+: 494
885	PEx5, Ex16	ESI+: 494
886	Ex709	ESI+: 469
887	Ex1	ESI+: 491
888	Ex1	ESI+: 509
889	Ex1	ESI+: 392
890	Ex1	ESI+: 392
891	Ex1	ESI+: 362
892	Ex709	ESI+: 451

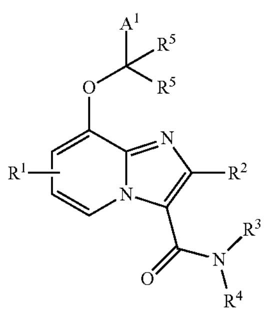
INDUSTRIAL APPLICABILITY

The compound of formula (I) has an sGC activation and can be used as an active ingredient of a pharmaceutical composition for treating or preventing sGC-related cardiovascular diseases, for example, hypertension, atherosclerosis, lumbar spinal canal stenosis, peripheral arterial diseases, as well as intermittent claudication and critical limb ischemia caused by the aforesaid peripheral arterial diseases, stable or unstable angina pectoris, heart failure, thrombosis, stroke, sexual dysfunction, pulmonary hypertension, or the like.

The invention claimed is:

1. A compound of formula (I)

(I)



wherein:

A^1 is cyclohexyl, or phenyl optionally substituted with one or more F atoms,

R^1 is H,

R^2 is R^0,

R^3 is H,

R^5 is H,

R^4 is $-Y-A^2$ or A^3,

Y is C_{1-10} alkylene optionally substituted with at least one group selected from Group G^2,

Group G^2 is $—CO_2H$ and —OH,

A^2 is H, cycloalkyl, pyridyl, or phenyl optionally substituted with a group selected from the group consisting of lower alkyl and $—CO_2H$,

A^3 is cycloalkyl selected from the group consisting of cyclopentyl, indanyl, dihydrocyclopentathienyl, dihydrocyclopentafuranyl, and dihydrocyclopentapyrrolyl, the above cycloalkyl is optionally substituted with at least one group selected from Group G^1, or piperidyl or pyrrolidyl each optionally substituted with at least one group selected from Group G^1,

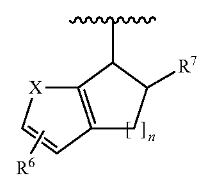
Group G^1 is R^0, halogen, $—CO_2H$, —OH, $—CO_2R^0$, —CN, $—NO_2$, phenyl, and $—SO_2—NH_2$, and

each R^0 is independently lower alkyl,

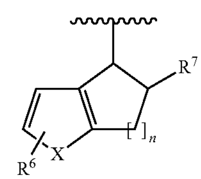
or a salt thereof.

2. The compound according to claim **1**, wherein A^1 is cyclohexyl, 2-fluorophenyl, 2,3-difluorophenyl, 2,6-difluorophenyl, or 2,3,6-trifluorophenyl, and R^4 is a group represented by any one of the following formulae (A), (B), (C), (D), (E), (F), and (G):

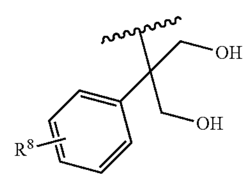
(A)



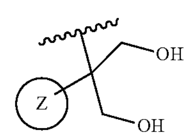
(B)



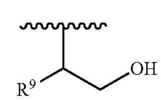
(C)



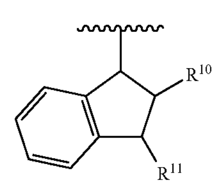
(D)



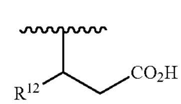
(E)



(F)



(G)



wherein

R^6 is H, halogen, or R^0,

R^7 is —CO_2H, —CO_2R^0, or —NO_2,

X is NH, NR^0, O, S, or —HC═CH—,

n is 1,

R^8 is H or lower alkyl,

Z is pyridyl,

R^9 is phenyl or lower alkyl,

R^{10} is H or —OH,

R^{11} is H or —OH, and

R^{12} is lower alkyl, cycloalkyl, or phenyl,

or a salt thereof.

3. The compound according to claim **2**, wherein

A^1 is 2,6-difluorophenyl,

R^2 is methyl,

R^4 is a group represented by the formula (A) or the formula (B),

X is —HC═CH—,

R^6 is F, and

R^7 is —CO_2H,

or a salt thereof.

4. The compound according to claim **2**, wherein R^2 is methyl and R^4 is a group represented by the formula (C) or the formula (D), or a salt thereof.

5. The compound according to claim **2**, wherein

A^1 is cyclohexyl or 2,6-difluorophenyl,

R^2 is methyl,

R^4 is a group represented by the formula (A) or the formula (B),

X is —HC═CH—,

R^6 is H, and

R^7 is —CO_2H,

or a salt thereof.

6. The compound according to claim **2**, wherein R^2 is methyl and R^4 is a group represented by the formula (E), or a salt thereof.

7. The compound according to claim **2**, wherein R^2 is methyl and R^4 is a group represented by the formula (F), or a salt thereof.

8. The compound according to claim **2**, wherein R^2 is methyl and R^4 is a group represented by the formula (G), or a salt thereof.

9. The compound according to claim **2**, which is selected from

the group consisting of:

(3 S)-3-({[8-(cyclohexylmethoxy)-2-methylimidazo[1,2-a]pyridin-3-yl]carbonyl}amino)-3-phenylpropanoic acid,

(1S,2R)-1-[({8-[(2,6-difluorobenzyl)oxy]-2-methylimidazo[1,2-a]pyridin-3-yl}carbonyl)amino]indane-2-carboxylic acid,

(1S,2R)-1-({[8-(cyclohexylmethoxy)-2-methylimidazo[1,2-a]pyridin-3-yl]carbonyl}amino)indane-2-carboxylic acid,

(1R,2S)-1-({[8-(cyclohexylmethoxy)-2-methylimidazo[1,2-a]pyridin-3-yl]carbonyl}amino)indane-2-carboxylic acid,

8-[((2,6-difluorobenzyl)oxy]-N-(1,3-dihydroxy-2-phenylpropan-2-yl)-2-methylimidazo[1,2-a]pyridine-3-carboxamide,

(1S,2R)-1-[({8-[(2,6-difluorobenzyl)oxy]-2-methylimidazo[1,2-a]pyridin-3-yl}carbonyl)amino]-7-fluoroindane-2-carboxylic acid,

(1S,2R)-1-[({8-[(2,6-difluorobenzyl)oxy]-2-methylimidazo[1,2-a]pyridin-3-yl}carbonyl)amino]-4-methylindane-2-carboxylic acid,

(1S,2R)-1-({[8-(cyclohexylmethoxy)-2-methylimidazo[1,2-a]pyridin-3-yl]carbonyl}amino)-5-fluomindane-2-carboxylic acid,

(1S,2R)-1-({[8-(cyclohexylmethoxy)-2-methylimidazo[1,2-a]pyridin-3-yl]carbonyl}amino)-7-fluoroindane-2-carboxylic acid,

(1R,2S)-1-({[8-(cyclohexylmethoxy)-2-methylimidazo[1,2-a]pyridin-3-yl]carbonyl}amino)-7-fluoroindane-2-carboxylic acid,

(1S,2R)-1-({[8-(cyclohexylmethoxy)-2-methylimidazo[1,2-a]pyridin-3-yl]carbonyl}amino)-4-methylindane-2-carboxylic acid,

(1S,2R)-1-[({2-methyl-8-[(2,3,6-trifluorobenzyl)oxy]imidazo[1,2-a]pyridin-3-yl}carbonyl)amino]indane-2-carboxylic acid,

8-[((2,6-difluorobenzyl)oxy]-N-[(1R)-2-hydroxy-1-phenylethyl]-2-methylimidazo[1,2-a]pyridine-3-carboxamide,

8-[((2,6-difluorobenzyl)oxy-N-[(1R,2R)-2-hydroxy-2,3-dihydro-1H-inden-1-yl]-2-methylimidazo[1,2-a]pyridine-3-carboxamide,

8-[((2,3-difluorobenzyl)oxy]-N-(1,3-dihydroxy-2-phenylpropan-2-yl)-2-methylimidazo[1,2-a]pyridine-3-carboxamide,

8-[((2,6-difluorobenzyl)oxy]-N-[1,3-dihydroxy-2-(pyridin-2-yl)propan-2-yl]-2-methylimidazo[,2-a]pyridine-3-carboxamide,

8-((cyclohexylmethoxy)-N-[(1R)-2-hydroxy-1-phenylethyl]-2-methylimidazo[1,2-a]pyridine-3-carboxamide,

8-[((2,6-difluorobenzyl)oxy]-N-[(2R)-1-hydroxypropan-2-yl]-2-methylimidazo[1,2-a]pyridine-3-carboxamide,

8-[((2,6-difluorobenzyl)oxy]-N-[(2R)-1-hydroxy-3-methylbutan-2-yl]-2-methylimidazo[1,2-a]pyridine-3-carboxamide, and

N-(1,3-dihydroxy-2-phenylpropan-2-yl)-8-[(2-fluorobenzyl)oxy]-2-methylimidazo[1,2-a]pyridine-3-carboxamide,

or a salt thereof.

10. The compound according to claim **2**, which is selected from

the group consisting of:

8-[((2,6-difluorobenzyl)oxy]-N-[(1R,2S,3 S)-2,3-dihydroxy-2,3-dihydro-1H-inden-1-yl]-2-methylimidazo[1,2-a]pyridine-3-carboxamide,

8-[((2,3-difluorobenzyl)oxy]-N-[(1R,2S,3 S)-2,3-dihydroxy-2,3-dihydro-1H-inden-1-yl]-2-methylimidazo[1,2-a]pyridine-3-carboxamide, and

N-[(1R,2S,3 S)-2,3-dihydroxy-2,3-dihydro-1H-inden-1-yl]-8-[(2-fluorobenzyl)oxy]-2-methylimidazo[1,2-a]pyridine-3-carboxamide,

or a salt thereof.

11. The compound according to claim **2**, which is selected from

the group consisting of:

8-[((2,6-difluorobenzyl)oxy]-N-[(1R,2S,3R)-2,3-dihydroxy-2,3-dihydro-1H-inden-1-yl]-2-methylimidazo[1,2-a]pyridine-3-carboxamide,

8-[((2,3-difluorobenzyl)oxy]-N-[(1R,2S,3R)-2,3-dihydroxy-2,3-dihydro-1H-inden-1-yl]-2-methylimidazo[1,2-a]pyridine-3-carboxamide, and

N-[(1R,2S,3R)-2,3-dihydroxy-2,3-dihydro-1H-inden-1-yl]-8-[(2-fluorobenzyl)oxy]-2-methylimidazo[1,2-a]pyridine-3-carboxamide,

or a salt thereof.

12. The compound according to claim **1**, which is selected from the group consisting of:

8-[((2,6-difluorobenzyl)oxy]-N-[(1r,3R,4S)-3,4-dihydroxy-1-phenylcyclopentyl]-2-methylimidazo[1,2-a]pyridine-3-carboxamide, and

8-[((2,6-difluorobenzyl)oxy]-N-[(1s,3R,4S)-3,4-dihydroxy-1-phenylcyclopentyl]-2-methylimidazo[1,2-a]pyridine-3-carboxamide,

or a salt thereof.

13. The compound according to claim **1**, which is selected from the group consisting of:

8-((cyclohexylmethoxy)-2-methyl-N-[(3S)-1-methylpiperidin-3-yl]imidazo[1,2-a]pyridine-3-carboxamide,

(3R)-3-({[8-(cyclohexylmethoxy)-2-methylimidazo[1,2-a]pyridin-3-yl]carbonyl}amino)-5-methylhexanoic acid,

8-((cyclohexylmethoxy)-N-(1,3-dihydroxypropan-2-yl)-2-methylimidazo[1,2-a]pyridine-3-carboxamide,

8-((cyclohexylmethoxy)-2-methyl-N-[(3S)-1-methylpyrrolidin-3-yl]imidazo[1,2-a]pyridine-3-carboxamide,

3-[((1S)-1-({[8-(cyclohexylmethoxy)-2-methylimidazo[1,2-a]pyridin-3-yl]carbonyl}amino)ethyl]benzoic acid,

8-[((2,6-difluorobenzyl)oxy]-N-(1-hydroxy-2-methylpropan-2-yl)-2-methylimidazo [1,2-a]pyridine-3-carboxamide,

8-[((2,6-difluorobenzyl)oxy]-N-[(1R,2S)-2,3-dihydroxy-1-phenylpropyl]-2-methylimidazo[1,2-a]pyridine-3-carboxamide,

(3R)-4-cyclobutyl-3-({[8-(cyclohexylmethoxy)-2-methylimidazo1,2-a]pyridin-3-yl]carbonyl}amino)butanoic acid,

8-[((2,6-difluorobenzyl)oxy]-2-methyl-N-[(3S)-1-sulfamoylpiperidin-3-yl]imidazo[1,2-a]pyridine-3-carboxamide, and

8-[((2,6-difluorobenzyl)oxy]-2-methyl-N-[(3S)-piperidin-3-yl]imidazo[1,2-a]pyridine-3-carboxamide,

or a salt thereof.

14. A pharmaceutical composition comprising the compound or a salt thereof according to claim **1**, and a pharmaceutically acceptable excipient.

15. A method for treating occlusive thrombotic vasculitis, peripheral arterial occlusive disease, intermittent claudication, critical limb ischemia, Raynaud's disease, Raynaud's syndrome, hypertension, or pulmonary hypertension, comprising administering to a subject an effective amount of the compound or a salt thereof according to claim **1**.

* * * * *